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ALIPHATIC NITROGENOUS FIVE-MEMBERED RING COMPOUNDS

(57) The present invention is to provide an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [i]:

$$R^2$$
-X-NH-CH₂-CO-N A [1]

wherein A represents -CH2- or -S-,

R1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkyl group, X represents -N(R3)-, -O- or -CO-, where R3 represents hydrogen atom or a lower alkyl group, and represents (1) a cyclic group which may be substituted, or (2) an amino group which may be substituted, or a pharmaceutically acceptable sait thereof, a method for preparing the above-mentioned compound and a pharmaceutical composition comprising the above-mentioned compound as an effective ingredient,

EP 1 325 910 A1

Description

TECHNICAL FIELD

[0001] The present invention relates to a novel aliphatic nitrogen-containing 5-membered ring compound having superior dipeptic/lipeptidase IV (DPPIV) inhibitory action that is useful as a pharmaceutical.

BACKGROUND ART

- [0002] Dipeptidylpeptidase IV (DPPIV) is a kind of serine protease that specifically hydrolyzes a dipeptide of Xaa-Pro or Xaa-Ala (where Xaa may be any amino acid) from the N terminus of a polypeptide chain.
 - [0003] There are various reports regarding the role of DPPIV (also called to as CD26) in the body and its relationship with diseases (Holst, et al., Diabetes, Vol. 47, pp. 1683-1670, 1998, Augustyns, et al., Current Medicinal Chemistry, Vol. 6, pp. 311-327, 1999; Meester, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999, and, Fleicher, et al., Immunol. Today, Vol. 15, pp. 180-184, 1994).
 - [0004] GLP-1 (glucagon-like peptide 1) is a peptide hormone that mainly acts in the pancreas after being secreted from the lower small intestine after meals, and primarily has the function of amplifying glucose-induced insulin secretion. In addition, there are several reports suggesting that GLP-1 has an appetite-suppressing action. DPPIV hydrolyzes GLP-1, forming an inactive or antagonistic optide.
- 20 [0005] Substances that inhibit the enzyme activity of DPPIV enhance the insulin secretion response to oral glucose loading by enhancing the action of intrinsic GLP-1, thereby improving impaired glucose tolerance.
 - [906] Consequently, DPPIV inhibitors are considered to be useful for the prophylaxis and treatment of diabetes (particularly type 2 diabetes), sic. Also, they are expected to be effective for the prophylaxis and treatment of other diseases induced or exceedabled by impaired glucose tolerance (including hyperglycemia (such as postprandial hyperglycemia).
- 25 perglycemia, hyperinsulinemia, diabetes complications (such as renal disorder and neurological disorder), hpid metabolism disorder and obesity, etc.).
 - [0007] Moreover, DPPIV inhibitors are also expected to be effective for the prophylaxis and treatment of diseases that are to be improved by onhancing the appolite suppressing action of GLP-1 (including overaeling and obesity, etc.). [0008] Also DPPIV (CD26) present on the surface of T cells is strongly upregulated following T cell activation, and plays an important role in the activation and proinferention of T cells. T cell activity is known to be suppressed when DPPIV (CD26) is blocked by antibodies or inhibitory substances. Also, there has been an interest in the correlation.
 - between this enzyme and the pathological state in collagen metabolism disorders and diseases associated with abnormal immunity. For example, the DPPIV (CD28) positive rate of peripheral blood T cells is elevated in rheumatold patients, and high leve's of DPPIV activity have been detected in the unrie of nephritis patients. Moreover, DPPIV (CD28) is also thought to play an important role in the entry of HIV into lymphocytos.
 - [0009] Consequently, substances that inhibit DPPIV (CD28) are expected to demonstrate prophylactic and therapeutic effects against diseases holuding autoimmune diseases (such as arthritis and ribermatoid arthritis), osteoporosis, acquired immunodeficiency syndrome (AIDS) and rejections of transplanted organs and tissues.

 [0010] On the other hand, as compounds having DPPIV inhibitory action, there are described 2-cyarcpyrrolidine
- derivatives having OPPIV inhibitory action in International Patent Laid-Open Publications Nos. WO98/19998 and WO00/34241.
 - [0011] The present invention provides a novel aliphatic nitrogen-containing 5-membered ring compound having an excellent DPPIV inhibitory action.

45 DISCLOSURE OF THE INVENTION

- [0012] As a result of earnest research to solve the above problems, the present inventors found a noval alightatic nitrogen-containing 5-membered ring compound having DPPIV inhibitory action, thereby accompilished the present invention.
- [0013] Namely, the present invention relates to an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [i]:

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wherein A represents -CH2- or -S-,

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R1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkyl group, X represents -N(R3), -O - or -CO., where R3 represents hydrogen atom or a lower alkyl group, and R3 represents (1) a cyclic group which may be substituted, where the cyclic group portion is

- (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or
- (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or
- (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

[0014] Although optical isomers based on an asymmetric carbon oan be present in the objective compound [] of the present invention, the present invention includes any of these optical isomers as well as mixtures thereof. In addition, although isomers (cis form or trans form) are also present based on the relative positions of substituents with respect to the standard plane of a cyclic group, the present invention also includes any of these isomers as well as mixtures thereof.

[0015] In the present invention, examples of a lower alkyl group, a lower alkylthic group, a lower alkylygy group and a lower alkylygy group bands a lower alkylygy group band a lower alkanoyl group and a lower alkanoyl group and a lower alkanoyl group and a lower alkanoylarino group include linear or branched groups having a 10 - action atomas, and particularly those having a 10 - action atomas, and particularly 30 - a fower optionality group and lower cyclosilkenyl group include those having 30 - a fower alkanoyle group include a lower alkanoyle group include a fower alkanoyle group include a fower alkanoyle group include those having 30 - a fower alkanoyle group include those having 30 - a fower alkanoyle group include those having 30 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include those having 20 - a fower alkanoyle group include 10 - a fower alkano

[0016] In the objective compound [i] of the present invention, examples of hydrogen atom or a lower alkyl group represented by R³ include hydrogen atom, methyl group, etc. Among them, hydrogen atom is more preferred.

[0017] In the compound [I] of the present invention, exemples of "hydrogen atom, a lower alkyl group, a hydroxy iower alkyl group or lower alkyl group and methoxymethyl group, hydroxymethyl group and methoxymethyl group. Among them, hydrogen atom is preferred.

[0018] In the compound [i] of the present invention, a cyclic group portion of "a cyclic group which may be substituted" represented by R2 includes

- (i) a monocyclic, bicyclic or tricyclic hydrocarbon group and
- (li) a monocyclic, bicyclic or tricyclic heterocyclic group,

[0019] Such monocyclic, blcyclic or tricyclic hydrocarbon groups include those having 3 to 15 carbon atoms, which may be partially or completely saturated.

[0020] Monocyclic hydrocarbon groups include those having 3 to 7 carbon atoms, examples of which include phenyl group, cyclohexyl group, cyclopentyl group, cyclopent

[0021] Bicyclic hydrocarbon groups include those having 9 to 11 carbon atoms, examples of which include an indanyl group, an indenyl group, an aphthyl group, a tatrahydronaphthyl group and partially or completely saturated cyclic arouse thereof, etc.

[0022] Tricyclic hydrocarbon groups include those having 12 to 15 carbon atoms, examples of which include a fluorenyl group, an enthryl group, a phenanthryl group and partially or compiletely saturated cyclic groups thereof, etc. 00231 Monocyclic blyclic or tricyclic heterocyclic groups include a monocyclic blyclic or tricyclic heterocyclic group

containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which may be partially or completely saturated.

[0024] Monocyclic heterocyclic groups include a heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atoms, oxygon atom and suffur atom and comprising of a saturated or unsaturated 5 to 7-membered from in a carrier or many containing the control of the con

[0025] Bicyclic heterocyclic groups include a heterocyclic group containing 11o 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two saturated or unsaturated 5- to 7-membered rings being fused, examples of which include:

45 an indolinyl group, an isolndolinyl group, an indolyl group, an indazolyl group, an isolndolyl group, a benzimldazolyl group, a thenpoyridyl group, a theosopyridyl group, a probapyridyl group, a groupyridyl group, a groupyridyl group, a groupyridyl group, a groupyridyl group, a chirollonyl group, a chroninyl group, a quinoxalinyl group, a quinoxalinyl group, a quinoxalinyl group, a chroninyl group, a chroninyl group, a groupyridyl group, a groupyridyl group, a chroninyl group, a chroninyl group, a groupyridyl group, a groupyridyl group, a chroninyl group, a groupyridyl groupyridyl

[0926] Tricyclic heterocyclic groups include a heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising three saturated or unsaturated 5- to 7-membered rings being fused, examples of which include:

a benzoxolanopyrimidyl group, a β-carbolinyl group, a carbazolyl group, a phenothiazinyl group, a phenoxazinyl group

and partially or completely saturated cyclic groups thereof, etc

[0027] Among those cyclic groups (monocyclic, bicyclic or tricyclic hydrocarbon groups or monocyclic, bicyclic or tricyclic heterocyclic groups),

- "(i) a monocyclic hydrocarbon group having 3 to 7 carbon atoms.
 - (ii) a bicyclic hydrocarbon groups having 9 to 11 carbon atoms,
 - (iii) a monocyclic heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, or
 - (iv) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused*

is preferred, examples of which include:

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'phenyl group, cyclohexyl group, cyclohentyl group, cyclopropyl group, an Indanyl group, an indenyl group, a naphthyl group, tetrahydronaphthyl, a pyrrollidnyl group, an indexolidnyl group, a naphthyl group, a trivial group, a pyrazolidnyl group, a pyrrolly group, a pyrro

50 [0028] Among them, more preferred examples include:

"phenyl group, cyclchevyl group, a pyrroldifnyl group, a telrazolyl group, a thenyl group, a thiazolyl group, a piperdyl group, a piperdyl group, a piperdyl group, a propholinyl group, a piperdyl group, a pyridyl group, a pentydroszopnyl group, an indolinyl group, an isoindolinyl group, a benzothionyl group, a thienopyridyl group, a pyrrolopyridyl group, a dihydropyrrolopyridyl group, a quinolyl group, an isocuinolyl group, a quinoxal'nyl group and partially or completely saturated cyclic groups thereof, etc.", and further preferred examples include:

"a pyrrolidinyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrmidinyl group, an indolinyl group, an isolndolinyl group, a pyrrolopyridyl group, a dihydropyrrolopyridyl

group and partially or completely saturated cyclic groups thereof, etc."

[0029] Among them, particularly preferred examples include: "1 pyrrolidinyl group, 1 piperialyl group, 1 piperazinyl group, 4-morpholinyl group, 4-morpholinyl group, 4-morpholinyl group, 4-morpholinyl group, 4-morpholinyl group, 2-solinylor-ly-group, 2-pyrimidinyl group, 2-solindollinyl group, 1-in-dollinyl group, 3-dirlydro-114-pyrmolol(3-b)pyrimid-2-y group etc."

[0030] "A cyclic group (a monocyclic, bicyclic or tricyclic hydrocarbon group or a monocyclic, bicyclic or tricyclic heterocyclic group) which may be substituted "represented by R² may be unsubstituted or have 1 to 3 substituents which are the same or different.

[0031] Substituents in the cyclic group are not particularly limited, and examples of which include substituents selected from the following "substituents of Group A". Among them, "substituents of Group A" are more preferred.

[0032] In the objective compound [i] of the present invention, "an amine group which may be substituted" represented by 92 may be unsubstituted or may be an amine group having 1 or 2 substituents which are the same or different (a mone-or disabstituted amine group).

[0033] Substituents in the amino group are not particularly limited, and examples of which include substituents selected from the following "substituents of Group B". Among them, "substituents of Group B" are more preferred.

[0034] "An amino group which may be substitured" represented by RP is preferably a substituted amino group (a mone- or di-aubstituted amino group), and more specifically "an amino group substituted by 1 or 2 substitutents which are the same or different and selected from the group consisting of a lower alkyl group (methyl group, etc.), a lower cycloally group, a lower alkyl group (methyl group, a byrytmidnyl group, a lower alkyl group, butly group, a byrytmidnyl group. a this-zoly group and a thirddiszoly group at a briddiszoly group at the standard product is preferred. Among them.

"(i) an amino group di-substituted by substituents which are the same or different and selected from a lower alkyl group (methyl group, ethyl group, bepropry) group, butyl group, etc.), a lower cycloalkyl group and a lower alkoxysubstituted lower alkyl group; or

(iii) an amino group mono-substituted by a substituent selected from a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group" is more preferred, and

"an amino group di-substituted by substituents which are the same or different and selected from a lower alkyl group (malty) group, altyl group, isoprapyl group, butyl group, etc.), a lower cycloalkyl group and a lower alkoxy-substituted lower alkyl group' is particularly preferred.

- --- Substituents of Group A:-----

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[0035] As substituents of Group A, the following substituents are mentioned:

a halogan atom (Cl. F, Br, etc.); cyano group; nitro group, oxo group, hydroxy group, carboxy group; oxidyl group; amino group; carbamoyl group; a lower alkanyl group; a lower alkanyl

a lower alkylthio group;

a lower alkylsulfonyl group:

a di-lower alkylamino-substituted lower alkoxy group;

a di-lower alkylaminocarboxy group;

a lower alkyl group substituted by group(s) selected from amino group, carbamoyl group, a halogen atom, hydroxy group, carboxy group, a lower alkoxy group and a mono- or di-substituted amino group

(substituents in the substituted amino group portion are not particularly limited, and examples of which include substituents of Group C mentioned below.):

a mono- or di-substituted amino group or a mono- or di-substituted carbamovi group

(substituents in the substituted amino group or substituted carbamoyl group are not particularly limited, and examples of which include substituents of Group C mentioned below.):

a substituted or unsubstituted lower cycloalkyl group,

a substituted or unsubstituted lower cycloalkyl-CO-,

a substituted or unsubstituted lower cycloalkyl-lower alkyl group,

a substituted or unsubstituted phenyl group,

a substituted or unsubstituted phenyl-O-,

a substituted or unsubstituted phenyl-CO-,

a substituted or unsubstituted phenyl-lower alkyl group,

a substituted or unsubstituted phenyl-O-lower alkyl group.

a substituted or unsubstituted phenyisulfonyl group.

- a substituted or unsubstituted phenyl-lower alkoxy group,
- a substituted or unsubstituted phenyl-lower alkoxycarbonyl group,
- a substituted or unsubstituted cycloalkenyl group (a cyclobutenyl group, etc.),
- a substituted or unsubstituted bicyclic heterocyclic group,
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group.
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O-,
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-,
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-lower alkyl group, and
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group
- (substituents in the substituted lower cycloalkyl group portion, substituted phenyl group portion, substituted lower cycloalkenyl group portion, substituted bicyclo heterocyclic group portion or substituted monocyclic 5- or 6-membered heterocyclic group portion are not perticularly limited, and examples of which include
 - a halogen atom (Cl. F, Br, etc.), cyano group, nitro group, oxo group and substituents in the substituents of Group C mentioned below, etc.

[0036] Also, a monocyclic 5- or 8-membered heterocyclic group portion includes a monocyclic 5- or 8-membered heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and specific examples include

a piperidyl group, a piperazinyl group, a morpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a thiadiazolyl group.

[0037] Also, a bix-yolic heterocyclic group portion includes a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- or 6-membered rings being fused, and examples of which include an isolnicitiny group, an indollinyl group, exit indollinyl group, exit indollinyl group, and examples of which include an isolnicitinyl group, as indollinyl group, exit in

---Substituents group A' (particularly preferred substituents of Group A):-----

[0038] As more preferable substituents of Group A, the following substituents are mentioned:

- a halogen atom (Cl, etc.); cyano group; nitro group; oxo group; carbamoyl group; a lower alkyl group; a lower alkoxy group; a lower alkanoyl group; a lower alkoxycarbonyl group; a lower alkoxy-substituted ornio group; a mono- or di-substituted armio group; a lower oxide/korabonyl-substituted armio group.
 - a mono- or di-substituted carbamoyl group (a phenyl-substituted carbamoyl group, etc.),
 - a lower cycloalkyl-CO-.

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- a substituted or unsubstituted phenyl group (phenyl group, a halophenyl group, etc.).
- a substituted or unsubstituted phenyl-lower alkyl group (a phenyl-lower alkyl group, a halophenyl-lower alkyl group, etc.),
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group (a thienyl group, etc.),
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O- (a pyrimidinyloxy group, at halopyrimidinyloxy group, atc.), and
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO- (a pyridylcarbonyl group, a thienylcarbonyl group, etc.).

(In the above description, each menocyclic 5- or 6-membered haterocyclic group portion includes a monocyclic 5- or 6-membered haterocyclic group containing 1 or 2 hotero aloms selected from nitrogon atom, oxygen atom and sullur atom, and exemples of which include a pyricyl group, a pyrinditinyl group, a thienyl group, etc.)

-----Substituents of Group B : -----

[0039] As substituents of Group B, the following substituents are mentioned:

a lower alkyl group; a lower alkoxy-substituted lower alkyl group; a lower alkoxycarbonyl-substituted lower alkyl group; a hydroxy lower alkyl group; a carboxy lower alkyl group;

a substituted or unsubstituted lower cycloalkyl group

a substituted or unsubstituted lower cycloalkyl-lower alkyl group,

a substituted or unsubstituted phenyl group,

a substituted or unsubstituted phenyl-lower alkyl group.

a substituted or unsubstituted bicyclic hydrocarbon group.

- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group.
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group, and
- a substituted or unsubstituted bicyclic heterocyclic group-lower alkyl group
- 5 (substituents in the substituted lower cycloalikyl group portion, substituted phenyl group portion, substituted bicyclic hydrocarbon group portion, substituted monocyclic 5- or 6-membered heterocyclic group portion or substituted bicyclic heterocyclic group portion are not particularly limited, and examples of which include substituents in the substituents of Group C mentioned below.

[0040] A bicyclic hydrocarbon group portion includes a bicyclic hydrocarbon group having 9 to 11 carbon atoms, and examples of which include an indanyl group, etc.

[0041] Also, a monocyclic 5- or 6-membered heterocyclic group portion includes a monocyclic 5- or 6-membered heterocyclic group containing 1 or 2 fistero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and examples of which include

a piseridyl group, a piperazinyl group, a morpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a pyrnolidinyl group, an imidaziolidnyl group, a pyrazolidinyl group, a pyrazolyl group, a thianyl gro

[0042] Also, a bicyclic haterocyclic group portion includes a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- or 6-membered rings being fused, and oxamples of which include a benzodioxolanyl group, etc.).

---- Substituents of Group B' (more preferred substituents of Group B) ; ------

[0043] As more preferred substituents of Group B, the following substituents are mentioned:

a lower alkyl group (methyl group, ethyl group, isopropyl group, butyl group, etc.), a lower cycloalkyl group, a lower alkoxy-substituted lower alkyl group, a pyrimidinyl group, a thiazolyl group, a thiadiazolyl group.

[0044] As particularly preferred substituents of Group B, the following substituents are exemplified:

[0046] In case that PA is a dis-ubstituted amino group, a lower alkly group (methyl group, athyl group, leopropyl group, butyl group, etc.), a lower cycloalky group and a lower alkoys-substituted lower alkyl group; and in case that RP is a mono-substituted amino group, a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group.

----Substituents of Group C : -----

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[0046] As substituents of Group C, the following substituents are mentioned:

35 a lower alkly igroup; a hydroxy-lower alkly igroup; a lower alkanory igroup; a lower cycloalkylcarbony group; a lower alkoxy group; a lower alkoxycarbony! group; a lower alkylsulfony! group; a di-lower alkyl-subatituted carbamoy! group; a di-lower alkylsmino-substituted lower alkanoy! group; and

a substituted or unsubstituted phenyl group,

a substituted or unsubstituted phenyl-O-.

a substituted or unsubstituted phenyl-CO-,

a substituted or unsubstituted phenyl-lower alkanoyl group,

a substituted or unsubstituted phenyl-lower alkyl group,

a substituted or unsubstituted phenyl-lower alkoxy group,

a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group,

a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-0- (a pyridyloxy group, etc.), a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO- (a pyridylcarbonyl group,

etc.), and
a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-substituted amino group (a pyri-

dylamino group, etc.) (substituents in the substituted phenyl group portion or substituted monocyclic 5- or 6-membered heterocyclic group portion are not particularly limited, and examples of which include

a halogen atom (Cl, F, Br, etc.), cyano group, nitro group, oxo group, a lower alkyl group, a lower alkoxy group, a lower alkoxy group, and a lower alkoxycarbonyl group, etc.

[0047] Also, a monocyclic 5- or 6-membered heterocyclic group portion includes a monocyclic 5- or 6-membered heterocyclic group containing 1 or 2 hetero atoms selected from filtrogen atom, oxygen atom and sulfur atom, and

a piperidyl group, a piperazinyl group, a morpholinyl group,

examples of which include

a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a fhiazolyl group, a thiadiazolyl group, a thienvi group, etc.)

[0048] In the objective compound [i] of the present invention, as R² when X is -N(R³)- or -O-, a cyclic group which may be substituted may be mentioned as a preferred example.

[0049] Also, in the objective compound [i] of the present invention, as R² when X is -CO-, there may be mentioned (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted are presented by the formula:

15 as preferred examples.

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[0050] Also, in the objective compound [i] of the present invention, among the two kinds of cis-trans isomers based on a cyclohexyl ring in the structure [i] as a standard plane, a trans-isomeric compound is more preferred from the viewpoint of obtaining higher DPPIV inhibitory activity. That is, among the objective compound [ii] of the present invention, a compound having the following partial structure:

or a pharmaceutically acceptable salt thereof is preferred.

[0051] In particular, for a compound in which the group X is -CO-, superiority of such trans isomer is remarkable.

[0052] As one compound group of the compounds of the present invention, among the compounds [], those in which so Re [s] (1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic heterocyclic group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

(2) an amino group having 1 or 2 substituents which are the same or different and selected from the substituents of Group B can be mentioned. (Compound Group 1)

[0053] Also, as other compound groups, among the compounds [i] or the above-mentioned Compound Group 1, the compounds in which R2 is

- (1) a cyclic group which may be substituted, where the cyclic group portion is selected from the following (i) to (iv):
- "(I) a monocyclic hydrocarbon group having 3 to 7 carbon atoms,
- (ii) a bicyclic hydrocarbon groups having 9 to 11 carbon atoms,
 - (iii) a monocyclic heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and
- (iv) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused; or
- (2) a substituted amino group;

can be mentioned (Compound Group 2).

[0054] Also, among the above-mentioned Compound Group 2, the compounds in which R2 is

(1) a cyclic group which may be substituted whorein the cyclic group portion is a group selected from henryl group, eycloehusly group, eycloehusly group, eycloehusly group, excloehusly group, an in-denyl group, a neatherly group, an in-denyl group, a neatherly group, a triangular group, an indiazolidinyl group, a pryratyl group, a manufazolidinyl group, a pryratyl group, a manufazolidinyl group, a pryratyl group, a pryratyl group, a triangular group, a middezolyl group, an acceptatyl group, an acceptatyl group, an acceptatyl group, a triangular group, a triangular group, a triangular group, a pryratyl group, a gyridyl gyridyl group, a gyridyl group, a gyridyl gyridyl gyridyl group, a gyridyl gyrid

an indolyl group, an indazolyl group, an isoindolyl group, a benzimidazolyl group, a benzotniazolyl group, a thienepyridyl group, a thienepyridyl group, a diprotepyridyl group, a diprotepyridyl group, a diprotepyridyl group, a diprotepyridyl group, a chromanyl group, a diprotepyridyl group, a diprotepyridyl group, a diprotepyridyl group, a diprotepyridyl group, a chromanyl group, a nephthyridinyl group and partially or completely saturated cyclic groups thereof; or (2) a substituted armino group can be mentioned (Compound Group 3).

[0055] Also, in Compound Group 3, as more preferred compound group, the compounds in which R2 is

(1) a cyclic group which may be subatituded, where the cyclic group portion is a group selected from the group consisting of heavily group, a cycloheavy group, a pyperdidinyl group, a tetrazolyl group, a funyl group, a thisayoly group, a piperidyl group, a piperidyl group, a pyriddidinyl group, a gwell gwell group, a gwell g

(2) a substituted amino group can be mentioned (Compound Group 4).

[0056] Also, in Compound Group 4, as more preferred compound group, the compounds in which R2 is

(1) a cycle group which may be substituted wherein the cycle group portion is a group selected from a pyrrollding forcup, a piperdyl group, a piperatyl group, a morpholingly group, a thiomorpholingly group, a thiomorpholingly group, a pyrindingly group, an inabilingly group, an isolindlingly group, a pyrindingly group, an inabilingly group, an isolindlingly group, and group and partially or completely saturated cyclic groups thereof; or

25 (2) a substituted amino group can be mentioned (Compound Group 5).

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[0057] Also, among the compounds [I], as another more preferred compound group, the compounds in which R2 is

a cyclic group which may have 1 to 3 substituents, which are the same or different, selected from the substituents
of Group A', where the cyclic group portion is selected from the group consisting of

a pyrolidinyl group, a pjerikyl group, a pjerazknyl group, a morpholinyl group, a thiomorpholinyl group, a pyrlolyl group, a pyrimidinyl group, an indolinyl group, an isolndolinyl group, a pyrmiopyridyl group, a dihydropyrmolopyridyl group and pari ally or completely saturated cyclic groups thereof; or

(2) an amino group substituted by 1 or 2 substituents, which are the same or different, selected from the substituents of Group B' can be mentioned. (Compound Group 6)

[0058] Also, among the compounds [ii], or among each of the above-mentioned Compound Groups 1, 2, 3, 4, 5 and 8, a compound group in which, when X is -N(R³)- or -O-, R² is a cyclic group which may be substituted can be mentioned. (Compound Group 7)

[0059] Also, among the compounds [I], or among each of the above-mentioned Compound Groups 1, 2, 3, 4, 5 and 6, a group of compounds in which, when X is -CD. R² is (1) a monocycle, bycycle or tricyclion introgen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, represented by the formula:

can be mentioned. (Compound Group 8)

[0060] Also, among the compounds [I] or the above-mentioned Compound Groups 1, 2, 3, 4, 5, 6, 7 or 8, as more preferred compound groups,

55 a compound group in which X is -CO- or -O- and A is -CH_{o-}:

a compound group in which X is -CO- or -O-, A is -CH2- and R1 is hydrogen atom;

a compound group in which X is -CO-, A is -CH₂- and R¹ is hydrogen atom;

a compound group in which X is -CO-, A is -CH₂-, R¹ is hydrogen atom and R² is a cyclic group which may be

substituted:

a compound group in which X is -CO-, A is -CH₂-, R¹ is hydrogen atom and R² is a substituted amino group;

a compound group in which X is -CO- or -O- and A is -S-:

a group of compounds in which X is -CO- or -O-. A is -S-and R1 is hydrogen atom:

a compound group in which X is -CO-, A is -S- and R1 is hydrogen atom;

a compound group in which X is -CO-, A is -S-, R1 is hydrogen atom and R2 is a cyclic group which may be substituted; a compound group in which X is -CO-, A is -S-, R1 is hydrogen atom and R2 is a substituted amino group, etc. may be mentioned.

10 [0061] Also, in each of the above-mentioned compound groups, as a more preferred compound group, a compound group having the following partial structure:

can be montioned.

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[0062] Also, among the compounds [i], the following compounds can be mentioned as examples of preferred compounds:

(S)-2-cvano-1-ftrans-4-(5-nitro-2-pyridylamino)-cyclohexylamino)acetylpyrrolidine: (S)-2-cyano-1-[trans-4-(5-cyano-2-pyridyloxy)-cyclohexylamino]acetylpyrrolidine; 25 (S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)-cyclohexylaminolacetylpyrrolidine; (S)-2-cyano-1-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylpyrrolidine; (S)-2-cyano-1-[trans-4-(5-bromo-2-pyrimidinyloxy)-cyclohexylamino]acetylpyrrolidine; (S)-2-cyano-1-[trans-4-(5-pyrimidinylaminocarbonyl)-cyclohexylaminolacetylpyrrolidine: (S)-2-cvano-1-[trans-4-(N-ethyl-N-methoxyethylaminocarbonyl)cyclohexylaminolacetylpyrrolldine: 90 (S)-2-cyano-1-itrans-4-(N-ethyl-N-isopropylaminocarbonyl)cyclohexylamino]acetylpyrrolldine; (S)-2-cyano-1-[trans-4-(N-methyl-N-butylaminocarbonyl)cyclohexylaminolacetylpyrrolidine; (S)-2-cyano-1-[trans-4-](S)-2-methoxymethylpyrrolidin-1-ylcarbonyl]cyclohexylamino]acety/pyrrolidine; (S)-2-cyano-1-[trans-4-(3-carbamoyipiperidinocarbonyl)cyclohexylamino]acetylpyrrolidine; (S)-2-cyano-1-[trans-4-(3-nltro-2-pyridylamino)cyclohexylamino]acetylpyrrolidine; 35 (S)-2-cyano-1-(trans-4-(4-acetylpiperazin-1-ylcarbonyl)cyclohexylaminolacetylpyrrolldine: (S)-2-cvano-1-(trans-4-(2-isoindolinvlcarbonyl)cyclohexylamInolacetylpyrrolldine: (S)-2-cyano-1-[trans-4-[4-(3-pyridylcarbonyl)piperazin-1-ylcarbonyl]cyclohexylamino]acetylpyrrolldine; (S)-2-cyano-1-(trans-4-[4-(3-thenoyl)piperazin-1-yl-carbonyl]cyclohexylamino)acetylpyrrolldlne; (S)-2-cyano-1-{trans-4-[4-(4-chlorophenyl)piperazin-1-ylcarbonyl]cyclohexylamino}acetylpyrrolldine; 40 (S)-2-cyano-1-[trans-4-(cis-2,6-dimethylmorpholinocarbonyl)cyclohexylaminolacetylpyrrolidine: (S)-2-cyano-1-[trans-4-(5-nitro-2-isoindolinvicarbonyl)cyclohexylaminolacetylpyrrolidine; (S)-2-cvano-1-(trans-4-(piperidinocarbony))cvclohexylamino)acetylpyrrolidine: (S)-2-cvanc-1-ftrans-4-(4-carbamoylpiperidinocarbonyl)cyclohexylamino)acetylpyrrolldine; (S)-2-cyano-1-[trans-4-(1-pyrrolidinylcarbonyl)-cyclohexylamino]acetylpyrrolidine 45 (S)-2-cyano-1-[trans-4-(4-cyclopropylcarbonylpiperazin-1-ylcarbonyl)cyclohexylaminojacetylpyrrolidine; (S)-2-cyano-1-[trans-4-(4-proplonylpiperazin-1-yl-carbonyl)cyclohexylamino]acetylpyrrolidine; (S)-2-cyano-1-[trans-4-(1-indoliny|carbonyl)cyclohexylamino]acetylpyrrolidine; (S)-2-cyano-1-[trans-4-(2,3-dihydro-1H-pyrrolo[3,4-b]pyrldin-2-ykarbonyl)cyclohexylamino[acetylpyrrolidine; (S)-2-cyano-1-[trans-4-[4-(2-pyrimidinyloxy)-piper|d|nocarbonyl]cyclohexylaminolacetylpyrrolldine: (S)-2-cyano-1-(trans-4-[4-(5-bromo-2-pyrimidinyloxy)-piperidinocarbonyl]cyclohexylamino]acetylpyrrolidine; (S)-2-cyano-1-(trans-4-(cis-3,5-dimethyl-4-benzylpiperazin-1-ylcarbonyl)cyclohexylamino|acetylpyrrolidine; (S)-2-cyano-1-[trans-4-(4-cyclohexylcarbonylamino-piperidinocarbonyl)cyclohexylaminojacetylpyrrolidine; (S)-2-cvano-1-(trans-4-[4-(N-phenylcarbamovl)-piperazin-1-ylcarbonyl[cvclohexylamino]acetylpyrrolldine: (S)-2-cyano-1-[trans-4-(4-ethoxycarbonylpiperazin-1-ylcarbonyl)cyclohoxylamino]acetylpyrrolidine; 55 (S)-2-cyano-1-(trans-4-[4-(2-thlenyl)piperidinocarbonylicyclohexylamino)acetylpyrrolidine: (S)-2-cyano-1-[trans-4-(1,1-dioxoperhydro-1,4-thiazin-4-ylcarbonyl)cyclohexylamino]acetylpyrrolidine;

(R)-4-cyano-3-[trans-4-(5-nitro-2-pyridylamino)cyclohexylamino]acetylthiazolidine; (R)-4-cyano-3-[trans-4-(5-cyano-2-pyridyloxy)cyclohexylaminolacetylthiazolidine:

- (R)-4-cyano-3-(trans-4-(dimethylaminocarbonyl)cyclohexylamino]acetylthiazolidine:
- (R)-4-cvano-3-ftrans-4-(2-isoindolinvlcarbonyl)cvclohoxylaminolacetylthiazolidine:
- (R)-4-cyano-3-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylthiazolidine; and
- (R)-4-cyano-3-[trans-4-(pyrrolidinylcarbonyl)cyclohexylaminolacetylthiazolidine.

[0063] The objective compound [i] or a pharmaceutically acceptable salt thereof of the present Invention has superior inhibitory action on the enzyme activity of DPPIV. They have superior inhibitory action especially on human DPPIV. In addition, they also exhibit high selectivity with respect to DPPIV (namely, type IV dispetityl/peptidase) in various serine proteases (e.g., plasmin, thrombin, protylendopeptidase, tryosin and dispetityl/peptidase II).

[0064] Also, the objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention improves insulin secretion response to oral glucose loading by means of its DPPIV inhibitory action.

[0065] Thus, the objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention is useful as prophylactic or therapeutic agents for diseases relating to DPPIV (diseases mediated by DPPIV), that is, diseases which is expected to be alleviated by inhibiting DPPIV enzyme activity.

[0066] Examples of such diseases include diabers (e.g., type 1 diaberes and type 2 diaberes), hyperglycemia (such as osptrandial hyperglycemia), hyperfirsulinemia, diaberes complications (such as renal disorder and neurological disorder), obesity, overesting, lipid motebolism disorder (such as hyperfipemia including hyperriglyceridemia and others), autoimmune diseases (such as arthrifis and neumaticid arthrifis), osteoporosis, acquired immunodeficiency syndrome (ADS) and rejection of transplanted organs and itssuer.

[0067] The objective compound [i] or a pharmaceutically acceptable salf thereof of the present invention is particularly useful as a prophylactic or therapeutic agent of diabetes (and particularly type 2 diabetes).

[0088] Also, the compound of the present invention has low toxicity, and thus, has a high degree of safety huged as a pharmaceutical compound. Also, it also demonstrates superior pharmacekinetic characteristic including backallability, in vitro metabolic stability (stability in human liver homogenates), P450 inhibitory action, protein binding capabilities, et al.

[0069] The DPPIV inhibitory action of the compound of the present invention as well as its pharmacoutical officacy (including anti-hyperglycemia effect and the effect of improving insulin secretion response to glucose loading) based on that action can be confirmed by known methods or methods equivalent to linear entohad (WOGM:1998 WOOC/ 34241; Holst, et al., Diabetes, Vol. 47, pp. 1683-1670, 1998; Augustyns, et al., Current Medicinal Chemistry, Vol. 6, pp. 311-327, 1999; Meester, et al., Immunol. Today, Vol. 20, pp. 337-376, 1999, and, Fleicher, et al., Immunol. Today, Vol. 15, pp. 180-184, 1994).

[0070] The objective compound [] of the present invention can be used for a pharmaceutical use either in a free form or in a form of a pharmaceutically acceptable salt. Examples of the pharmaceutically acceptable salt of the compound [] include an inorganic acid salt such as hydrochloride, surfate, phasphate or hydrobromide, and an organic acid salt such as acceptate, furnerate, oxisite, citrate, methanesulfonate, benzenesulfonate, toeylate or maleste, etc. in addition, in case that a compound has a substituent(s) such as carboxyl group, a salt with a base (for example, in a skall metal salt such as a coldum salt, a potassium salt, etc., or an alkaline earth metal salt such as a calcium salt and the like) may be manifonad.

[0071] The objective compound [i] or a pharmaceutically acceptable salt thereof of the present invention includes its internal salt, an adduct, a solvate and a hydrate.

[0072] The objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention can be administered orally or parenterally and used as commonly used pharmaceutical preparations such as a tablet, granule, cassule, powder, injection solution and inhalant. For example, the compound of the present invention can be used with an excipiont or a diluent acceptable for general pharmaceuticals such as a binder, disintegrator, extender, filler and lubricant, to form a proparation according to the usual method.

[0073] The administration does of the objective compound [1] or a pharmacoutically acceptable salt thereof of the present invention may vary depending on the administration method, age, weight and condition of a patient, and it is generally about 0.01 to 300 mg/kg, particularly preferably about 0.1 to 30 mg/kg per day.

[0074] The objective compound [i] of the present invention can be prepared according to the following (Process A) and (Process B), but it is not limited to those processes.

(Process A)

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[0075] The objective compound [i] of the present invention can be prepared by reacting a compound represented by the formula [ii].

$$Z^1$$
-CH₂-CO-N A [II]

wherein Z1 represents a reactive residue and A has the same meaning as defined above, with a compound represented by the formula [III]:

$$R^2-X NH_2$$
 [III]

wherein R1, R2 and X have the same meanings as defined above, or a salt thereof, and optionally, by making the product into a pharmaceutically acceptable salt.

[0076] As examples of the sait of the compound [III], a sait with an inorganic acid such as hydrochloride and sulfate, or a sait with an inorganic base such as an alkali metal sait and an alkaline earth metal sait can be used.

[0077] As the reactive residue of Z¹, commonly used reactive residues such as a halogen atom, a lower alkylsulfonyloxy group and an arylsulfonyloxy group can be used, among which the halogen atom is particularly preferred.

25 [0078] The reaction of the compound [ii] with the compound [iii] or the saft thereof can be carried out in a suitable solvent or without solvent in the presence or absence of an acid acceptor.

[0079] As the solvent, any solvents may be suitable as long as it does not adversely affect to the raction, and, for example, accoloritiel, methand, ethanoi, isoproyal actional, proxyl alcohol, accorbone, dimethyliormamida, dimethyl suitoxidd, strarhydrofuran, ether, cloxane, ethyl acctate, toluene, methylene chloride, dichloroethane, chloroform or a mixed solvent of these solvents can be suitably used.

[0080] This reaction suitably proceeds at 0 to 120°C, particularly at room temperature to 80°C.

[0081] As the acid acceptor, an inorganic base (for example, alkali metal hydride such as sodium hydride, alkali metal acmonate such as sodium acrononate and potassium carbonate, alkali metal alkoxide such as sodium methoxide, alkali metal such as sodium, and alkali metal provide such as sodium hydroxide, alkali metal such as sodium such as sodium hydroxide, alkali metal such as sodium hydroxide, alkali mydroxide, alkali mydroxide, alkali metal such as sodium hydroxide and potassium hydroxide, alkali metal alkali metal such as sodium hydroxide, alkali metal alkali metal such as sodium hydroxide alkali mydroxide such as sodium hydroxide and such as sodium hydroxide and such as sodium hydroxide, alkali metal hydroxide such as sodium hydroxide such as sodium hydroxide such as sodium hydroxide alkali metal hydroxide such as sodium hydroxide, alkali metal alkacité such as sodium hydroxide, alkali metal hydroxide such as sodium hydroxide, alkali metal hydroxide such as sodium h

(Process B)

40 [0082] In addition, among the objective compound [I] of the present invention, the compound represented by the formula [I-a]:

$$R^{21}$$
-CO- NH -CH₂-CO- N [I-a]

wherein R^{21} represents (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, and represented by the formula:

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$$\binom{n}{n}$$

and R^1 and A have the same meanings as defined above, can be prepared by reacting a compound represented by the formula [IV]:

HOOC-
$$\begin{array}{c} R^1 \\ N-CH_2-CO-N \\ R^4 \end{array}$$
 [IV]

wherein R⁴ represents a protective group for an amino group, and R¹ and A have the same meanings as defined above.

or a salt thereof with the compound represented by the formula [V]:

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or a salt thereof to obtain a compound represented by the formula [VI]:

wherein R1, R4, R21 and A have the same meanings as defined above.

or a salt thereof, and by removing the protective group for the amino group (R4) from the product, and optionally, by making the product into a pharmaceutically acceptable salt.

[0083] As examples of saits of the compounds [IV] to [VI], a sait with an inorganic acid such as hydrochloride and sulfate, or a sait with an inorganic base such as an alkali metal sait and an alkaline earth metal sait can be used.

[0084] As the protective group for the amino group of R4, any of the commonly used protective groups for the amino group such as I-butosycarbonyl group, benzyloxycarbonyl group, benzyloxycarbonyl group, benzyloxycarbonyl group, cet. can be suitably used.

[0085] The reaction of the compound [IV] or a salt thereof with the compound [V] or a salt thereof can be carried out in a suitable solvent or without solvent in the presence or absence of a condensing agent.

[0088] As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, accentratile, methand, ethand, isopropyl alcohol, perpyl alcohol, accenter, dimethylformamida, tetrahor-furan-cutran, ether, dioxene, ethyl accetate, toluene, methylene chloride, dichloroethane, chloroform or a mixed scilvent of these solvents can be suitably used.

[0087] This reaction suitably proceeds at 0 to 120°C, particularly at room temperature to 80°C,

[0088] For the condensing agent, O-benzotriazol 1-yl-N,N,N',N'-tetramethyluroniumhexalluorophosphato, DCC (dicyclohoxylcarbodlimidd), EDC (1 ethyl-3-(3-dimethyl-amlnopropyla-abdellimide), -bloroformatos (for example, ethyl chloroformata end isobuty (chloroformate) and carbonyldimiciazole can be suitably used.

[0089] Also, for promoting the reaction, additives such as base (sodium carbonate, sodium hydrogencerbonate, triethylamine, pyridine, 4-dimethylaminopyridine, disopropylethylamine, 1.8-diszabicyclot(5.4.0]undec.7-ene, etc.), 1-hydroxylecordinacyle, 1-hydroxylecordinacylecordina

[0990] The subsequent removal of the protective group (R²) for the amine group of the compound [VI] can be carried out according to the conventional method, and it can be carried out, for example, in a suitable solvent or without servert by an addit trament, base treatment or catalytic reduction.

[0091] As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, methanol, eithanol, isopropyl alcohol, propyl alcohol, dioxane, methylene chloride, chloroform, diohlorestiane, ethic, (tetra-pytofrujan, eithyl alcotta, (bluene) or a mixed solvent of these solvents can be suitably used.

[0092] This reaction suitably proceeds at -78 to 80°C, particularly at 0°C to room temperature.

[0093] As the acid, an inorganic acid such as hydrochloric acid, sulfuric acid, etc., and an organic acid such as acetic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, etc. can be sulfably used.

2 [0044] As the base, an inorganic base (for example, alkell metal hydride such as sodium hydride, etc., alkali metal cardonate such as sodium carbonate, potassium carbonate, etc., alkali metal alkoxide such as sodium nethoxide etc., alkali metal such as sodium hydroxide, potassium hydroxide, etc.) or an organic base (for example, triethylamine, disspropriethylamine, morpholine, N-methylmorpholine, pyridine, piperidine, dimethylamiline, disspropriethylamine, morpholine, N-methylmorpholine, pyridine, piperidine, dimethylamiline, dimethylaminopyridine, etc.) can be suitably used.

[0995] The catalytic reduction can be carried out by suitably using palladium-carbon, palladium hydroxide-carbon, platinum oxide or Raney nickel under hydrogen atmosphere.

[0096] The starting material [II] of the present Invention can be prepared, for example, according to the method described in International Petent Publications Nos. WO 98/19998, WO 00/34241, Reference Examples (Reference

20 [0097] For example, the compound [ii] can be obtained by reacting a compound represented by the formula [10]:

wherein A has the same meaning as defined above, with a compound represented by the formula [11]:

wherein \mathbb{Z}^2 and \mathbb{Z}^3 represent reactive residues which may be the same or different, in the presence of an acid acceptor (for example, triethylamine) to obtain a compound represented by the formula [12]:

$$Z^2$$
-CH₂-CO-N A [12]

wherein Z2 and A have the same meanings as defined above.

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and treating the product with a dehydrating agent (for example, phosphorous oxychloride, trifluoroacetic anhydride, etc.) according to the conventional method

[0098] As the reactive residue of Z² or Z³, the same reactive residue commonly used as in the above Z¹ can be suitably used.

[0099] The starting material [III] can be prepared, for example, by the same method as described in Reference Examples (Reference Examples 3 to 14) mentioned below.

[0100] For example, the compound [III] in which X is -N(R3)-or -O- can be prepared by reacting a compound represented by the formula [13]:

$$V^1$$
 NH_2 [13]

wherein V1 represents -NH(R3)- or hydroxy group, and

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R1 and R3 have the same meanings as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [14]:

$$R^2-Z^4$$
 [14]

wherein Z4 represents a reactive residue and R2 has the same meaning as defined above.

in the presence or absence of an acid acceptor (for example, an organic base such as triethylamine, discopropylathylamine, etc., and an inorganic base such as sodium hydride, potassium carbonate, etc.), and, if necessary, by removing the protective group for the amino group according to the convolutional method.

[0101] As the protective group for the amino group, any of the same protective groups commonly used as in the above R4 can be suitably used.

[0102] As the reactive residue of Z⁴, the same reactive residues commonly used as in the above Z¹ can be suitably used

[0103] For example, the compound [iii] in which X is -CO-and R2 is a group represented by the formula:

can be produced by reacting a compound represented by the formula [15]:

$$V^2 \longrightarrow \begin{array}{c} R^1 \\ NH_2 \end{array} \qquad [15]$$

wherein V² represents -COOH and R¹ has the same meaning as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [16]:

wherein R²² represents (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, represented by the formula:

and forms a cyclic or straight amine together with hydrogen atom,

or a salt thereof, in the presence of a condensing agent (1-ethyl-3-(3-dimethylaminopropy)lcarbodimide, etc.) and, if necessary, by removing the protective group for the amino group according to the conventional method.

[0104] Or else, the compound [III] in which X is -CO- can be obtained by reacting a compound represented by the

formula [17]:

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$$Z^5$$
-OC- NH_2 [17]

wherein Z⁵ represents a reactive residue and R¹ has the same meaning as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [18]:

$$R^2$$
-Sn(R^5)_a [18]

wherein R5 represents a lower alkyl group and R2 has the same meaning as defined above, in the presence of a palladium catalyst (for example, dichlorobis(triphenylphosphine)palladium, etc.)

In the presence of a plantaum relatives (or example, unknown by promptines mapparation), the control promptines of the protective group of the amino group, any of the same protective groups commonly used as in the above 27 eV can be suitably used. Also, as the reactive residue of 25, the same reactive residues commonly used as in the above 27 can be suitably used.

[0106] Or else, the compound [III] in which X is -N(R³)- can be prepared by reacting the compound represented by the formula [19]:

$$O = \begin{array}{c} R^1 \\ NH_2 \end{array}$$
 [19]

wherein R¹ has the same meaning as defined above, an amino group-protected material thereof or a salt thereof with the compound represented by the formula [20]:

wherein V3 represents -N(R3)H and R2 has the same meaning as defined above.

In the presence of a reducing agent (sodium triacetoxyborohydride, etc.) and, if necessary, by removing the protective group for the amino group according to the conventional method.

[0107] As the protective group for the amino group, any of the same protective groups commonly used as in the above R⁴ can be suitably used.

[0108] The starting materials [10] to [20] can be prepared according to known methods or in the same manner as described in Reference Examples mentioned below.

[0109] In order to obtain a transform of the starting material [iII] taking a cyclohexane ring as a standard plane, each transform of the starting cyclohexane compounds (the compounds [13], [15], [17], etc.) may be used.

[0110] Also, the starting material [IV] can be prepared, for example, in the same manner as in the process described in Example (Example 6-1, (1) to (3)) mentioned below or in accordance with these processes, as shown in the following figure. (In the figure, Z⁸ represents a reactive residue, R⁴ represents a protective group for an amino group and other symbols have the same meanlines as defined above.)

[0111] As the reactive residue of Z⁶, the same reactive residues commonly used as in the above Z¹ can be suitably used.

[Compound IV]

[0112] The compound [i] of the present invention or its starting material prepared according to the above is isolated in a free form or as a sait thereof, and purified. The sait can be prepared by subjecting to the sait-forming treatment conventionally used.

[0113] Isolation and purification can be carried out by applying the usual chemical operations such as extraction, concentration, crystallization, filtration, recrystallization, various kinds of chromatographies and the like

[0114] In the compound of the present invertion, optical isomers such as racemic isomers, optically active isomers, disastersomers, etc. can be present alone or as mixtures thereof. A stereochemically pure isomer can be derived by using a stereochemically pure starting material or by separating an optical isomer according to the general separation process for racemic resolution. Also, disastersomeric mixtures can be separated according to the conventional method, for example, fractional cystallization of by chromostography.

EXAMPLES

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[0115] The present invention will be described in detail by referring to the following Examples but these Examples do not intend to limit the present invention.

Example 1a-1

- 38 [0118] A acetonitrile-methanol solution containing 100 mg of (s)-1-bromacestyl-2-cyanopyrrolidine (Reference Example 1 mentioned below) and \$27 mg of N-Fisthrot-2-pyridy1-trans-1.4-cyclobroxancidamine (Reference Example 1 mentioned below) was etimed at room temperature for 15 hours. Water was added to the reaction mixture and the mixture was extracted with nibroform. After the extract was dried over socialum suitate, the solvent was removed under reduced pressure. The residue was purified by did column chromatiography (solvent: 0 to 10% methanol-chloroform) do toltain an oily product. The oily product was dissolved in 0.5 mil of ethyl acetate-0.5 mil of chloroform, and then 1.0 mil of 2th hydrochloric acid-other and 2 mil of other were successively added thereto. Precipitates were collection by filtration and washed with either to obtain (5)-2-cyanol-1-trans-4-(6-intro-2-pyridylaminol-yciohexylaminol-acetylpyrro-lidra-diffyrochloride (Eckmeple 4-1 in Table 1-a). Examples 1-a L2 to 16-152.
- [0117] Using (S)-1-bromoscelyl-2-cyanopyrrolidine and corresponding starting materials, they were treated in the same manner as in Example 1a-1, compounds of Tables 1a to 1d shown below (Examples 1a-2 to 1a-89, 1b-1 to 1b-71, 1b-1 to 1b-52 and 1d-1 to 152) were obtained. Incidentally, the corresponding starting materials were obtained by the similar method as described in Reference Examples mentioned below, by known methods or by a method in combination of these methods.
- [0118] Provided that the compound of Example 1d-77 was obtained by using trans-4-(1-piperazinylcarbonyl)cyclohoxylamine as a starting material.
 - [0119] Also, the compound of Example 10-39 (namely, (S)-2-cyano-1-(Irans-4-(IN-carboxymethy-I-N-methylamino) carborn)[-j-cylohevylamino] earlypyrrolliden-lydyrochioride) was oblained by treating the compound of Example 10-38 (namely, (S)-2-cyano-1-(Irans-4-(IN-tert-butoxycarbonymethyl-N-methylamino)carbonyllcyclohexylamino]acetyloyr-rollidine) with Uffuoroacetic acid, followed by treatin with Nortochioric acid.
- [0120] Also, the compound of the Example 1d-14 (namely, (S)-2-cyano-1-[trans-4-(1-piperaziny)carbony))cyclohexylaminoj-acety/cyrrolidine-dihydrochlor/de) was obtained by treating a free form of the compound of Example 1d-70 ((S)-2-cyano-1-[trans-4-(4-benzyloxycarbonyl-1-piperazinylcarbon-y)cyclohexylaminojacety/cyrrolidine) with trimethylallyl loidie.

Examples 2-1 and 2-2

[0121]

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(1) A mixture of 600 mg of 4-tert-butoxycarbonylamino-4-methylcydohoxanone (the compound of Reference Exemple 6-1, (3)), 783 mg of social triacetoxyborohydride, 343 mg of 3-cyanoaniline, 159 mg of accide acid and 6 ml of dichlorcethane was stirred at room temperature for 16 hours. The mixture was diluted with an aqueous saturated socium hydrogencarbonate solution and then extracted with chloroform. The extract was dired over anhydrous sodium sulfate and the solvent was removed under roduced presence. The residue was purified by silica gel column chromatography (solvent: hexane-ethyl acotate (4:1) to (1:1)) to obtain 304 mg of N-tert-butox-yearbonyl-1-methyl-6-4/3-cyano-phenylamino)-1-cyclohexylamine.

(2) 243 mg of N-tert-butoxycarbonyl-1-methyl-c-4-(3-cyanophenylamino)-r-1-cyclohexylamine obtained in the above (1) was stirred in a mixture of 2 mi of 4N hydrochloric acid/ dioxane and 2 mi of ethanol at room temperature for 15 hours.

After the reaction mixture was concentrated, to the residue were acided 320 mg of (6)1-bromeacetyl-2-cyanopyrrolldine, 0.6 ml of trethylamine, 9.5 ml of acetonitrile and 1 ml of methanol and the mixture was ditured with an aqueous saturated sodium hydrogenearbonate solution and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the selvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent chloroform-methanol (60.1)) to obtain 154 mg of the compound, which was then treated with hydrochlorid sold to yield (6)2-cyano-114-methyl-c4-(2-cyano-phenylamino)-r1-cyclohexylamino]acetylpyrrolldine-dhydrochloride (Table 2: Example 2-1).

(3) Using N-tert-butoxycarbonyl-1-methyl-t-4-(3-cyanophenylamino)-r-1-cyclohexylamine obtained in the above (1), it was treated in the same manner as in (2), (5)-2-cyano-1-1-methyl-c-4-(3-cyano-phenylamino)-r-1-cyclohex-ylamino-3-excetylpyrrolid-e-ditydrochothod (Example 2-2 in Table 2) was obtained.

Examples 2-3 to 2-8

[0122] Using corresponding starting materials, they were treated in the same manner as in Examples 2-1 to 2-2, compounds of Examples 2-3 to 2-8 shown in Table 2 were obtained.

Example 3-1

35 [0123]

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(1) In water was dissolved 5.0 g of trans-4-ethoxycarbonylcyclohexylamine dihydrochloride, and after the solution was made basic by adding potassium carbonate, the solution was extracted with chloroform. The oxtract was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. A mbture of the residue, 5.1 g of o toluensulfonic acid monohydrate and 50 ml of allyl alcohol was refluxed for 48 hours. The reaction mbture was concentrated, and then, diluted with chloroform. The chloroform solution was washed with an aqueous potassium carbonate solution, water and brine, dried over anhydrous sodium sulfate.

and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent. chloroform methanol-aqueous ammonia (600:10:1)) to obtain 3:29 g of Irans-4-(2-propenyloxycarbonyl) cyclohexylamine.

(2) A mixture of 507 mg of the compound obtained in the above (1), 400 mg of (S)-1-bromaeselyt-2-oyanopyrrolidine, 714 mg of NN-dilsopropyleitylsamine and 4 ml of acetoritrile was stirred at 50°C for 12 hours. After cooling
to room temperature, 476 mg of NN-dilsopropyleitylsamine, followed by 4 ml of acetoritrile solution containing 803
mg of 01-ten-buyldicarbonate were added to the reaction mixture, and the mixture was stirred at room temperature
for 3 hours. After the reaction mixture was concentrated, the concentrate was diulded with entry acetals. The
acetals solution was washed with an aqueous 10% cliric acid solution, water and brine, dried over anhydrous
acid was utilate, and concentrated under reduced pressure. The residue was purified by sitiling agl fillagh orbinatography (solvent: chloroform-methanol (100:1)) to obtain 658 mg of (5) 2-dyano-1-[N-tert-butoxycarbonyl-trans4/2-poceparisoyscarbonylvscolbers/aminolace/bilvyrolinginals.

(3) A mixture of 600 mg of the compound obtained in the above (2), 165 mg of tetrakis(triphenylphosphine)palladium, 271 mg of arminoilium formate and 6 ml of dioxane was slirred at 50°C for 1 hour. After cooling, the reaction mixture was pound into water and extracted with chloroform. The extract was washed with bithe, ofter over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (solvent: chloroform-methanol (50·11) to obtain 394 mg of (5)-2-cyano-1-(N-tert-butoxycarbony-trians-4-carboxycotlobxylamino)acetylpyrrollidine.

(4) A solution of 2 min NN dimethylformamide containing 150 mg of the compound obtained in the above (3), 64 mg of 2-eminomethylpydrian i. 14 mg of 1-ethylfor-3-d-dimethylaninopropyl-sexobidimide and 80 mg of 1-hydroxy-benzotriazole was stirred at room temperature for 24 hours. An aqueous saturated sodium hydrogencarbonate solution was actided to the reaction mixture and the mixture was extracted with chlorodome. The extract was washed with brine and died over anhydrous sodium suitate and the solvent was removed under reduced pressure. The residue was dissolved in 5 mil of acetonatile, and 1 mil of a necenotrial solution of 116 mg of trimethylsily lodde was added drophylic to the solution inder lec-ocoling, and the mixture was street al room temperature for 30 minutes. To the reaction mixture were added methanol and water, and after stirring for a while, the mixture was solutifalized with an equeous saturated sodium hydrogencarbonate solution, water and brind, chiral over anhydrous acidium suitated and the solution was column suitated. The residue was purified by diol chromatography (solvent: chloroform) to obtain an oily product. The oily product was dissolved in 1 mil of ethly sociate, and then, to, 5 mil of 118 mg of 100 mg of 100

35 Examples 3-2 to 3-12

[0124] The compounds of Examples 3-2 to 3-12 in Table 3 were obtained in the same manner as in Example 3-1 (4), using (5)-2-cyano-1-(N-tert-butoxycarbonyl-trans-4-carboxycyclohexylamino)acetylpyrrolidine (the compound of the above Example 3-1 (3)) and the corresponding starting materials.

Examples 4-1 to 4-32

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[0125] A solution of 2 milof acetonitrile-1 milof methanol containing 100 mg of (R)-3-chloroscetyl-4-cyanothiazolidine (the compound of Reference Example 2 mentioned below) and 372 mg of N-(5-nitro-2-pyridyl)-trans-1,4-cyclohoxanodiamine was stirred at room tomporature for 15 hours.

[0126] Water was added to the reaction mixture and the mixture was extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by diel column chromatography (solvent: 0 to 5% methanol-chloroform) to obtain an oily product. The oily product was dissolved in 0.5 ml of ethly acetate-0.5 ml of chloroform, and 1.0 ml of 2N hydrochloria acid-ether was added thereto, followed by 2 ml of ether. Pre-pridates were collected by filtration and washed with ether to obtain 173 mg of (R)-4-cyano-3-(Irans-4-(5-nitro-2-pyridylarninol)epichosylaminol-acetylhiazolidine dihydrochloride (Example 4-1 in Table).

[0127] Also, the compounds of Examples 4-2 to 4-32 in Table 4 were obtained in the same manner as mentioned above, using the corresponding starting materials.

Reference Example 1

[0128] According to the process described in the literature (WO 98/19998), (S)-1-promoacetyl-2-cyanopyrrolidine

was obtained by reacting L-profineamide (commercially available product) and bromoacetyl bromide, followed by dehydration. Reference Example 2

[0128] L-thioprolineamide hydrochloride was synthesized according to the process described in the literature (Ashworth et al., Bioorg, Med. Chem Lett.] Vol. 6, pp. 2745-2748, 1999, 2.38 in 10 chloroscepty children as added to a solution of 150 ml of diphloromethane containing 5.00 g of L-thioprolineamide hydrochloride thus obtained and 8.67 ml of triethylamine under lice-cooling, and the instruct was sirred at the same temperature for 1 hour. To the reaction mixture was added a dictionomethane solution containing 4.6 ml of pyridine and 8.4 ml of strittion-actic anyloride, and the mixture was further sirred at room temperature for 1 hour. The reaction mixture was washed with an aqueous 10% HCls obtain and vater, died over anylorous reggeneems usulfate, (litered and concentrated under reduced presure, and subsequently, the residue was crystallized from either to obtain 4.82 g of (R)-3-chloroscetyl-4-cyanothiazolidine as veltow-brownish crystals. Reference Examples 3.1 in 3.40

[0130] A solution of 5-nitro-2-chloropyridine (2.50 g) and trane-1.4-cyclohexanediamine (5.40 g) in ethanol (15 mi)letralhydroturan (10 mi) was stirred at room temperature for 5 days. The pracipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by siting agl column thromatography (solvent: chloroform-methanol-concentrated aqueous ammonia (20:4:1)) and crystallized from ethyl acetate to obtain N-5-nitro-2-cyribly-trane-1.4-cyclohexanodiamine (Reference Example 3-1 in Table 5).

[0131] Also, the compounds of Examples 3-2 to 3-40 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials.

Reference Examples 3-41 to 3-44

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[0132] A N.N-dimethylacetamide (30 ml) solution containing 4-nitrofluorobenzene (1.69 g) and trans-1,4-cyclohexaned amine (4.1 g) was stirred at 144°C for 3 days. After cooling, an aqueous saturated potassium carbonate solution was added to the reaction solution, and the reaction mixture was extracted with brilly acetate. The extract was added to the reaction solution, and then. The solvent was removed under reduced pressure. The residue was purified by silica gel fisats column chromatography (solvent chloroform-methanol-ammonia (90:10:11)), and the solvent was removed to obtain trans-N-(4-nitrophoryl)-1,4-cyclohoxanediamine (Reference Example 3-41 in Table 5) (2.31 g). [0133] Also, the compounds of Examples 3-42 to 3-44 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting meterials.

Reference Examples 3-45 to 3-47

[0134] 25 mL of an ethanol solution containing 1.23 g of N-tert-butoxycarboryl-trans-1.4-cyclohexanediamine, 1.0 g of 2-chiloro-3-nitro-pyridine 1-oxide and 700 mg of dimethylaminopyridine was refluxed under argon atmosphere for 2 hours.

[0138] After cooling, the reaction solution was concentrated under reduced pressure, the residue was dissolved in chordorm, washed with water, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The obtained residue was purified by silica gel flash column chromatography (solvent: chiordorm-methanol (30:1)) to obtain red powder. The resulting compound was dissolved in 5mL of trifluoracerdo acid and the solution was sirred at room temperature for 5 hours. After the solvent was removed under reduced pressure, the residue was purified by silica gel flash column chomatography (solvent: aqueous ammonia-saturated chiordorm-methanol (10:1)) to obtain 110 grid N-(3-ntropyridina-1-oxid-2-yl-trans-1.4-cyl-obexanediamine (Reference Example 3-45 in Table 5). [0138] Also, the compounds of Examples 3-46 to 3-47 in Table 5 were obtained in the same manner as mentioned above, using corresponding starting materials.

Reference Examples 3-48 to 3-49

[0137] In the mixed solvent of 5 m of ethanol and 4 m lof tetrahydrofuran were dissolved 168 mg of N-tert-butoxy-carboryl-trans-4 (cholbror-3-pyridazinyl)aminolyciohoxylamine, 16 reference Example 3-48) and 0.5 m lof triothyl-amine. To the solution was added 5 m grid 10% palladium archon and the mixture was stirred under hydrogen amosphere with normal pressure at room temperature for 1 day. Alter the catalyst was removed by fittration, the solvent was removed, and the residue was stirred in 2 m lof trifluoroncetic acid for 3 hours. The solvent was removed, and consider the solution was added to the residue, the mixture was extracted with chloroform and dried over anhydrous socium unifate. Subsequently, the solvent was removed under reduced pressure to obtain 61 mg of trans-4/byridazin-9-ylaminolyciohoxylamine (Reference Example 3-48 in Table 5).

[0138] Also, the compound of Example 3-49 in Table 5 was obtained by treating the corresponding starting material (Reference Example 3-47) in the same manner as mentioned above.

Reference Examples 3-50 to 3-58

[0139] Also, the compounds of Examples 3-50 to 3-58 in Table 5 were obtained in the same manner as in Reference Example 9-50 or Reference Example 9-50.

Reference Example 3-59

[0140] Ethyl 4-chlore-2-phenyl-5-pyrimidinecarboxylate and N-tert-butoxycarbonyl-trans-1,4-cyclohexanediamme were reacted in othanol in the presence of dimethylaminopyridine in the same manner as in Reference Example 3-49 to obtain N-tert-butoxycarbonyl-trans-4-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinylamino)cyclohexylamina

[0141] The compound was treated in the same manner as in Reference Example 9-56 (1) and (2) to obtain trans-4-(5-morpholinocarbonyl-2-phenyl-4-pyrimidinylamino)cyclohexylamine (Reference 3-59 in Table 5).

Reference Example 4

[0142]

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(1) To 150 ml of a tetrahydrofuran suspension containing 10 g of trans-4-aminocyclohoxanol was added 15ml of fiothlyamine, 50 ml of a tetrahydrofuran solution containing 2-othoro-5-nitropydine was turther added thereto under ice-cooling, and then, the mixture was stirred at corn temperature for 18 hours. Water was added to the reaction mixture and the mixture was extracted with othoroform. The extract was washed with brine, dried over anhydrous solution suifate, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent: ethyl acetate-hexane (2:1)) to obtain 8.52 g of trans-4-(5-nitro-2-yrid/alminolyciclohaxanol.

(2) To 10 ml of a dichloromethane solution containing 1.0 g of the compound obtained in the above (1) was added 1.8 ml of triethylamine, 0.65 ml of methanesultoryl chloride was further added thereto under ice-cooling, and the mixture was stirred for 1 hour. An acqueous saturated solium bioarbonato solution was added to her saction mixture and the mixture was extracted with chloroform. The oxtract was washed with water and brine, dried over anhydrous solium suitate, and then, the solvent was removed under reduced pressure. 1.3 7 g of solium aride was added to a solution of the residue dissolved in 10 ml of dimetrylformarmide and the mixture was stirred at 50°C for 3 days. Aftercooling, and auguous saturated solium bioarbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium suifate, and then, the solvent was removed under reduced pressure. The readule was purified by silics gel flesh column chromatography (solvent: ethyl acetate-hexane (1:5)) to obtain 758 mg of cis4-azdde-N_(6-niro-2-pyridylcyclohazy-

(3) A solution comprising 10 mt of tetrahydrofuran-1 mt of water, containing 640 mg of the compound obtained in the above (2) and 704 mg of triphenylphosphine was stirred at room temperature for 2 days. The reaction mixture was concentrated, and the residue was purified by sill ong off lish oclurn chromatography (solvent: chyl acetatimethanol (10:11) to obtain 631 mg of N-(3-nitro-2-pyridyl)-cis-1,4-cyclohexanodlemine (the compound of Reference Example 4 in Table 5).

Reference Examples 5-1 to 5-6

[0143]

(1) in 600 mL of dimethylformamide were suspended 60.0 g of trans-4-tent-butoxycerbonylaminocydolnay/methanesulfonate and 20.1 g of sodium azide and the suspension was stirred at 90°C for 6 hours. The reaction mixture was poured into water and extracted with ethyl acotate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 47.9 g of cis-4-azida-N-(ent-butoxy-canonylycychokaystamin).

(2) in 8 mL of tetrahydrofuran were suspanded 500 mg of the compound obtained in the above (1) and 100 mg of palladium-carbon (well) and the suspansion was vigorously stirred under hydrogen atmosphere at room temporature for 1.5 horse. During the course, hydrogen in the system was replaced twice. The insolubles were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gol chromatography (solvent: chloroform-methanol (20:1), followed by chloroform-methanol-aqueous ammonia (100:10: 1)) to obtain 355 mg of N-tet-fluotycarbonyl-cis-1,4-cycolex-arediamine.

(3) A suspension comprising 10 mL of 2-propanol, 2.0 g of the compound obtained in the above (2), 1.63 g of 2-chloro-3-nitropyridine and 1.95 mL of disopropylethylamine was stirred at 80°C for 1 day. After the reaction

mixture was concentrated under reduced pressure, water was added thereto and the mixture was extracted with cottact. The extract was washed with brine, died over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silfice gel chromatography (solvent chloroform, followed by chloroform-cthyl accetate (7.1)). To a suspension of the resultant compound in ethanol was added hydrochloric accid-doxene, the mixture was stirred at room temperature for 18 hours, and the precipitates were collected by filtration to obtain 2.15 g of N-(3-nitro-2-pyridyl)-cis-1,4-cyclohexaned amine dihydrochloride (Reference Example 5-1 in Table 5).

[0144] Also, the compounds of Reference Examples 5-2 to 5-6 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials. Reference Example 6-1

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(1) According to the process described in the literature (JP83-118577), methyl 1.4-cloxaspira(4.5)decan-5-carbox-ylate was reacted with methyl idde in the presence of LDA (lithium discoproplamide) to obtain methyl 8-methyl-1.4-dioxaspira(4.5)decan-5-carboxylate (the compound (1) of the above figure).
(The starting materials were synthesized according to the process described in the literature by Rosemmund et al. (Chem. Ber., 1975, Vol. 108, pp. 1871-1893) and the literature by Black et al. (Synthesis, 1981, p. 329).)

(2) A mixture of 3.80 g of the compound obtained in the above (1), 3.55 g of sodium hydroxide, 16 mL of methanol and 25 mL of water was refluxed for 2 hours. The reaction mixture was ice-cooled, adjusted its pH to 5 by 2N hydrochloric acid and an aqueous 10% citric acid solution, and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain 3.46 g of 8-methyl-1,4-dioxespiro[4.5]decan-8-carboxylic acid (the compound (2) of the above figure). (3) A mixture comprising 16.19 g of the compound obtained in the above (2), 24.51 g of diphenylphosphoryl azide, 9.00 g of triethylamine and 160 mL of toluene was refluxed for 2.5 hours. The reaction mixture was ice-cooled, washed with an aqueous saturated sodium hydrogencarbonate solution, water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. To a solution of the resulting compound in 100 mL of dimethylacetamide was gradually added 9.55 g of potassium tert-butoxide under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice-water, and the precipitated crystals were collected by filtration, washed with water and dried. To a solution of the resulting compound in 100 mL of tetrahydrofuran was added 100 mL of an agueous solution containing 30.87 g of p-toluenesulfonic acid hydrate, and the mixture was stirred at room temperature for 16 hours. The mixture was diluted with an aqueous saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure

to obtain 10.41 g of 4-tert-bubxycarbonylamino-4-methyloydohaxanone (the compound (3) of the above figure).

(4) A mixture comprising 10.41 g of the compound obtained in the above (3), 11 of a dedium trinactoxylorohydride, 5.10 mL of benzylamine and 150 mL of methylene chloride was stirred at room temperature for 18 hours. The mixture was diluted with an arqueous saturated adouth hydrogeneatbonate solution and extracted with orbity accesses. The extract was weshed with water and brins, dired over anhydrous solution solitate, and the solvent was removed under reduced pressure. To a solution of the resulting compound in 16 mL of methanol was acided 3.32 g of p-tolumeasullon a calid hydrate, followed by 160 mL of sheet. The precipitates were collected by littration, washed with either and critical to obtain 7.49 g of N-benzyl-t-4-test-bubxycarbonylamino-4-methyl-r-1-cyclohoxylamino-p-tolumeations at the compound (4) of the above figure).

(5) A mixture comprising 18.83 g of the compound obtained in the above (4), 5.0 g of 10% palladium-carbon and 400 mL of methanol was stirred under hydrogen atmosphere (1 atm) for 24 hours. 10% palladium-carbon was removed by filtration and the filtrate was concentrated. The resulting residue was dissolved in a mixture of 50 mL of an aqueous 10% sodium hydroxide solution and 300 mL of other, the other layer was washed with water and brine, offied over arthydrous sodium suifalle, and the solvent was removed under reduced pressure to obtain 6.87 g of 14-1ert-butoxycarbonylamino-4-mothyth-1-cyolohexylamine (the compound (5) of the above fours).

(6) The filtrate in the step of the above (4) was treated with an aqueous sodium hydroxide solution and extracted with chloroform. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was applied to NH-silica gel column chromatography (solvent: hexane-eityl acetate (30:1 to 3:1) to obtain N-benzyl-o-4-tert-butoxycarbonylamine-4-mathyl-r-1-cy-clohexylamine. Then, this compound was treated in the same manner as described in the above (6) to obtain c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine (the compound (6) of the babve figure).

Reference Example 6-2

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5 [0145] In the same manner as in Reference Example 6-1 (1) to (5) or (6) except for using benzy oxymathyl chlorida instead of methyl lodide in the step of Reference Example 6-1 (1), 1-4-ert-butoxycarbonylamino-4-hydroxymethyl-1cyclohexylamine or c-4-ter-butoxycarbonylamino-4-hydroxymethyl-1-teyclohexylamine was obtained.

[0146] Also, in the same manner as in Reference Example 6-1 (1) to (5) or (6) except for using methoxymethyl of the latest of the step of Reference Example 6-1 (1), it-4-tert-butoxycarbonylamine-4-methoxymethyl-r-1-cyclohexylamine or 2-4-tert-butoxycarbonylamino-4-methoxymethyl-r-1-cyclohexylamine was obtained.

Reference Examples 7-1 to 7-18

[0147] A mixture comprising 1.70 g of 1-41-art-butoxycarbonylar-nino-4-melityl-1-1-cyclohexylamine (the compound obtained in the above Reference Example 6-16)). 20.4 g of 2-chirorpyrimidine, 3.24 m. J. of 10 incorpoylathylamine and 19 m.L. of 2-propanol was refluxed for 12 hours. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, critical over anylorous sodium suitate, and the solvent was removed under reduced pressure. The residue was purified by allos gel column chromatography (solvent: ethyl acetate-hexane (30:70 to 50:50). The resulting compound was dissolved in 4 mit of discone, to 1 m.L. of 4 hylorich loric acid-discone was added thereto, and the mixture was stirred for 6 hours. The reaction mixture was diluted with eher and the precipitated crystale were oldected by filteration and washed with either. The resulting crystale were oldected to water, which was asturated with potasse um carbonate, subsequently extracted with chloroform. The extract address over anylorous sodium sulfate, and the solvent was removed under reduced pressure to obtain 587 mg of 1-metryl-4-1-2-pyrimidnysmino-j-1-recyclohoxylamine (Reference Example 7-1 in Table 5).

5 [0148] Also, the compounds of Reference Examples 7-2 to 7-5 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials.

[0149] Also, the compounds of Reference Examples 7-6 to 7-9 in Table 6 were obtained in the same manner as mentioned above, using c-4-tert-buloxycarbonylamine-4-methyl-r-1-cyclohexylamine (the compound obtained in the above Reference Example 6-1, (6)) and the corresponding starting materials.

[0150] Also, the compounds of Reference Examples 7-10 to 7-18 in Table 5 were obtained in the same manner as mentioned above, using t- or c-4-tert-butoxycarbonylamino-4-hydroxymethyl-r-1-cyclohoxylamine (Reference Example 6-2) and the corresponding starting materials.

Reference Examples 7-19 to 7-23

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[0151] 4-tart-Butoxycarbonylamino-4-methylcyclohexanone (the compound (3) of Reference Example 6-1) and the corresponding starting materials (an amine compounds) were reacted in the presence of sodium triscetoxyborrhydride at room temperature for 16 hours under stirring, and then, an actio treatment of the reaction mature was carried out to

remove a protective group (t-butoxycarbonyl group), to obtain the compounds of Reference Examples 7-19 to 7-23 in Table 5. Reference Examples 8-1 to 8-4

(1) To 100 ml of a methylene chtoride solution containing 16,93 g of 4-flart-burbxyearbonylarmine) pcyclehexanone and 10,55 ml of N-methylbencylamine was added 19,88 g of solution traceloxyborybdriod under loce-booling, and the mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with an aqueous sodium hydrogeneuronnile solution and extracted with ethyl aceiste. The extract was weethed with water and brine, draed over anhydrous sodium suifate, and then, the solvent was removed under reduced pressure. The resulting residue was expended in hexare and collected by filtration. This mother liquor was concentrated, and the residue was purified by NH-siles galchromatography (solventh hexane-ethyl sociated (97.3 to 81.7), and the residue was further suspended in hexane and collected by filtration, whereby it was combined with the product previously obtained by filtration to 10.15.5 to

A suspension of 13.53 g of this compound and 2.00 g of palladium hydroxide-carbon suspended in methanol was subjected to catalytic hydrogenation under normal prossure at room temperature over 5 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to obtain 9.93 g of N-tertbutoxycartonyi-N-methyl-trans-1,4-cyclohevanediamine.

(2) The compound obtained in the above (1) and the corresponding starting materials (chloride) were used and reacted under reflux in 2-propanel in the presence of disopropylethylamine for 12 hours as in Reference Example 7-1, and the resulting compound was subjected to acid treatment with hydrochloric acid, and then, neutralized with potassium carbonate to obtain the compounds of Reference Examples 8-1 to 8-4 in Table 5.

Reference Examples 9-1 to 9-45

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[0152] 2.04 g of 80 % sodium hydride was gradually added to 160 ml of a tetrahydrofuran solution containing 1,0.0 g of trens4-(in-th-utoxycarbonylamino)sycholexanol and 7.35 g of 2-chiore-6-tinopydride, and 30 mL of demetrylauloxide was further added thereto, and then, the mixture was slirred at room temperature for 1 day. The reaction mixture was poured into water and othered with chloroform. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was applied to silica gid column chromatography (solvent-chloroform atone to chloroform-thyl acetate (2011). The obtained powder crystal were suspended in ethyl acetate-hexane mixed solution and collected by filtration to obtain 12.20 g of trans4-tert-butoxycarbonylamino-4-(6-rittro-2-pyridyloxy)-cyclohoxane. To 10 ml of an ethanol suspension containing 800 mg of this compound was added 2 in of 2R hydrochoric acid-dioxene solution, and the mixture was stiffred at room temperature for 18 hours. The precipitates were collected by filtration to 6.0 scila 58 mg of trans-4-(6-nitro-2-pyridyloxy)-cyclohoxylamin-hydrochloride (Reference Example 9-1 in Table 6).

25 [0153] Also, the compounds of Reference Examples 9-2 to 9-45 in Table 8 were obtained in the same manner as mentioned above, using the corresponding starting materials. Reference Examples 9-46 to 9-47

[0154] 60% sodium hydride was added to 10 mil of a tetrahydrofuran suspension containing 1.00 g of trans-4-amino-cyclohaxano hydrocholroise and the mixture was refuxed for 1 hour. After cooling to room temperature, 2-otheropyrindine was slowly added thereto and the mixture was spoured into fee-cold water and extracted with chloroform. The extract was washed with brine and drided over enhydrous sodium suffact, and then, the solvent was removed under reduced pressure. The residue was purified by NH-silica got column chromatography (solvent: ethyl acetate-hexane (1-4) to chloroform alone) to obtain 788 mg of trans-4-(2-pyrindflory/oxy)-cyclohexylamine (Reference Example 9-46 in Table 6).

[0155] Also, the compound of Examples 9-47 in Table 6 was obtained in the same manner as mentioned above, using the corresponding starting materials.

Reference Example 9-48

[0156] In the same manner as in Roforence Example 9-1, trans-1-lert-butoxycarbonylamino-4/3-hitro-2-pyridyloxy)cyclohoxane was obtained. Subsequently, a suspension of 3.35 g of this compound in 30 ml of chancl was stirred at
50°C, and 155 mg of palladium-authon (dry) and then 1.8 ml of hydrazine monohydrate were added thereto. After the
mature was stirred for 10 minutes, 185 mg of the remaining palladium-carbon was added thereto and the mixture was
refluxed for 40 minutes. After the reaction mixture was cooled to room temperature, the insolubles were removed by
filtration and the filtrate was concentrated under reduced pressure. The resulting residue was crystallized from ethanoi5 water (1:1) and the crystals were collected by filtration to obtain 2.58 g of trans-1-tert-butoxycarbonylamino-4-(3-amino2-pyridyloxyloyclohexane.

[0157] Then, hydrochloric acid-dioxane was added to an ethanol solution of this compound to subject to acid treatment to obtain trans-4-(3-amino-2-pyridyloxy)cyclohexylamina-hydrochloride (Reference Example 9-48 in Table 6).

Reference Example 9-49

[0158] In the same manner as in Reference Example 9-1 by using trans 4-(tert butoxycarbonylamino)cyclohexanol and the corresponding starting materials, trans-4-(5-ethoxycarbonyl-2-methylthiopyrimidin-4-yloxy)cyclohexylamine hydrochloride was obtained.

[0159] The hydrochloride compound was made into an aqueous solution, and the solution was treated with potassium carbonate and extracted with chloroform to obtain its free form (Reference Example 9-49).

Reference Examples 9-50 to 9-54

10 [0160] In 50 mL of chloroform was dissolved 2.75 g of N-tert-buoxyanthoryl-trans-4.5-ethoxyachbonyl-2-methyliane (accompound of Reference Example 9.49 point or deprotection (hydrochorios accid discane treatment)). 1.73 g of 75%-m-chloroperbenzoic acid was added to the solution, and the mixture was stirred at room temperature for 50 minutes. Then, 1.14 g of direstlynamine hydrochoriode and 2.78 mL of triethylamine were added thereto and the mixture was further stirred for 50 must. An aquecus saturated accidum hydropercetronate solution was added to the reaction mixture, and the mixture was stirred. Then, the chloroform layer was collected by separation, dried over anhydrous socialism sulfate and the sclevant was removed under reduced pressure. The residue was purified by silica gel flash chromatography (solvent: haxane-chloroform (60.50 to 100:00) to obtain 2.74 g of N-tert-butoxycar-bonyt-trans-4.5-echoxycaronyl-2-dimentlylaminop-pyrindiat-4-yloxycyclopkyralmine.

[0161] This compound was deprotected by treating with hydrochloric acid-dioxane, and subsequently neutralized with potassium carbonate to obtain trans-4-(5-ethoxycarbonyl-2-(dimethylamino)pyrimidin-4-yloxy)cyclohexylamine (Reference Example 9-50 in Täble 6).

[0162] Also, the compounds of Reference Examples 9-51 to 9-54 in Table 6 were obtained in the same manner as mentioned above.

25 Reference Examples 9-65 to 9-57

[0163]

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(1) In 15 mL of ethanol was dissolved 2.875 g of N-Iert-butoxycarbonyl-trane-4-[5-ethoxycarbonyl-2-(dimethylamino)-pyrimidin-4-yloxylgcylochexylamine (the compound of Reference Example 9-60 prior to deprotection treatment), 327 mL of an aqueous SN-4-sodium hydroxide solution was added thereto at room temperature, and the mixture was sitred overnight. The reaction mixture was ciliuted with water, and then, citric acid was added thereto until the solution became neutral. The precipitated cypistials were collected by littlantion, washed with water and dried under reduced pressure to obtain 2.015 g of N-Iert-butoxycarbonyl-trans-4-[5-carboxy-2-(dimethylamino)pyrimidin-4-lyoxylcyclboxylamino).

(2) The compound obtained in the above (1) was used as a starting material and reacted with a starting amine compound in the same manner as in Reference Example 11-1. The resulting compound (hydrochloride) was made into an acueous solution, and the solution was treated with potassium cerbonate and extracted with chloroform to obtain a fee form.

f01641 Thus, the compounds of Reference Examples 9-55 to 9-57 in Table 6 were obtained.

Reference Examples 9-58 to 9-64

5 [0165]

(1) 0.44 mil of DMSO was slowly added dropwise to 10 ml of a methylene chloride solution containing 0.526 ml of exally chloride under argon gas atmosphere et.-2°°C. After 15 minutes from the completion of the exidition, 30 ml of a methylene chloride suspension containing trans-4-tert-butoxycarbonylaminocyclohexanol in was added dropwise, and further 30 minutes later, 2.52 ml of intellytamine was soldard theretio and the mixture was stirred at 7.8°°C for 30 minutes and at 0°C for 15 minutes. An aqueous sodium buserbonate solution was added to the reaction mixture and the mixture was extracted with chloroform. The extract was dried over anhydrous socium suifate, and then, the solvent was removed under roduced pressure. The resulting refule was suspended in a hexane-so-propyl other mixed solvent and collected by filtration to obtain 0.903 g of 4-(tert-butoxycarbonylamino)cyclohexanone.

(2) To 350 ml of a tolurene solution containing 33.05 g of the compound obtained in the above (1) was added dropwise 313 ml of 1.0 M dilsobutyl aluminum hydride-toluene solution at -78°C, and the mixture was sittred at the same temperature for 4 hours. After an excessive reagent was decomposed by adding 33 ml of methat of the same temperature for 4 hours. After an excessive reagent was decomposed by adding 33 ml of methat of the same temperature for 4 hours. After an excessive reagent was decomposed by adding 38 ml of methat of the same temperature for 4 hours.

dropwise to the mixture, 100 ml of water was added thereto, and the mixture was attred for 1 hour. The precipitated insolubles were removed by filtration. The organic layer of the filtrate was excated and dried over emitydrous accilum sulfate. The solvent was removed under reduced pressure, the resulting residue was suspended in chloroform-isopropyl either mixed so vent under heating and the insolubles were removed by filtration. The filtrate was concentrated, and then, the same operation was performed with isopropyl either. The resulting filtratio was concentrated and the residue was purified by silica gel flash column chromatography (solvent: ethyl accitate-hexane (1: 2 to 1:11)), and the obtained colorises crystate were lurther suspended in hexane-isopropyl either mixed solvent under healting and subjected to litration at 0°C to obtain 6.95 g of cis-4-tert-butoxycarborylaminocyclonexanel. (3) The compounds of Reference Examples 9-1, using the above-obtained cis-4-tert-butoxycarborylaminocyclohexanel and the corresponding starting materials.

Reference Example 10-1

5 [0166]

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(1) A mixture comprising 9.13 g of 4-tent-butoxycarbonyl-amino-4-methylcyclohexanone, 3.05 g of sodium borohydride and 100 mL of Isopropyl alcohol was stirred at room temperature for 1 hour. Under ice-cooling, the reaction mixture was diluted with an equeous saturated armnonium chloride solution and extracted with eithyl sectate. The resulting extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 9.20 g of a mixture of t-4-tent-butoxycarbonylamino-4-methyl-1-ovclohexanol and o-4-tent-butoxycarbonylamino-4-methyl-1-ovclohexanol and o-4-tent-butoxycarbonylamino-4-methyl-1-ovclohexanol.

(2) A mixture comprising 9.20 g of the compound obtained in the above (1), 8.26 g of p-methoxypenzoic acid chloride, 5.93 g of dimethylaminopyridine and 100 mL of methylenechloride was refluxed for 20 hours. After cooling, the reaction mixture was weshed with an aqueous saturated sodium hydrogenacroancate solution, an aqueous 10% citric acid solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed. The residue was crystallized from n-hazane to obtain 0.88 g of c-4-tert-butoxycarbonylamino-4-methyl-C-(4-meth-oxybenyl-archive)-1 cyclotexanol (cis compound).

Also, the residue was purified by silica gel column chromatography [solvent: ethyl scetate/n-hexane (1/10)] to obtain 3.50 g of a mixture (1.5) of the above compound (cis compound) and t-4-tert-butoxycarbonylamino-4-methyl-0-14-methoxychenylcarbonyl)-r-1-cyclohexanol (trans compound).

(3) A mixture comprising 10.88 g of the cls compound obtained in the above (2), 8.10 g of sodium hydroxide, 150 mL of methanol and 120 mL of water was heated at external temperature of 75°C for 1 hour. After cooling the reaction mixture, the solvent was removed under reduced pressure and extracted with ethyl accisate. The extract was was had with an aqueous saturated sodium hydrogencarbonate solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 6.61 g of c-4-tert-but/cxycar-bonylamino-4-mixthy-ri-q-velohexanol.

(4) In the same manner as in the above (3) by using 3.50 g of the mixture (1:5) of cis form and transform obtained in the above (2), 1.77 g of t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol was obtained.

Reference Examples 10-2 to 10-8

[D167] The compounds of Reference Examples 10-2 and 10-3 in Table 6 were obtained in the same manner as in Reference Example 9-1 by using t-4-letr-butoxycarbonylamino-4-methyl-t-1-cyclohexanol (Reference Example 10-1 (4)) and the corresponding starting materials. Also, the compounds of Reference Examples 10-4 to 10-8 in Table 6 were obtained in the same manner as mentioned above by using o-4-tert-butoxycarbonylamino-4-methyl-t-1-cyclohexanol (Reference Example 10-1 (3)) and the corresponding starting materials.

Reference Examples 11-1 to 11-38 and 12-1 to 12-96

[0188] A mixture comprising 600 mg of trans-4-(tent-butoxy-carbonylamino)cyolohoxanecarboxylic acid, 250 mg of N-methyl-benzylamine, 434 mg of 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochorde, 308 mg of 1-hydroxy-benzotrazol and 5 ml of NN-dimethylformamide was stirred at room temperature for 15 hours. The reaction mixture was mado basic by adding an aqueous sodium hydrogencarbonate solution, and extracted with eithyl acotate. The extract was weather with where and brine, died over anhydrous sodium solitate, and then, the solvent was removed under reduced pressure to obtain 891 mg of N-benzyl trans-4-tert-butoxycarbonylamino-N-methylcyclohoxanecarbox-arrido. A mixture comprising 970 mg of ins compound, 5 mL of 4N-hydrochloric acid-dioxane and 5 ml of dioxane was stirred at room temperature for 12 hours. The reaction mixture was concentrated to obtain 585 mg of trans-4-arrino-N-

benzyl-N-methylcyclohexanecarboxamide hydrochloride (Reference Example 11-1 in Table 7).

[0169] Also, the compounds of Reference Examples of 11-2 to 11-38 and 12-1 to 12-96 in Tablo 7 and Tablo 8 mentioned below were obtained in the same manner as mentioned above by using the corresponding starting amine compounds (stight) that in amine compounds or cyclic secondary armine compounds such as a piperialrie compound, a piperazine compound etc.). (Provided that in case of free compounds, they can be obtained by saturating an aqueous solution of a hydrochloride sait compound with potassium carbonate, and after extracting the solution with chloroform, driving the extract over soldium sulfate and removant he solvent under reduced prossure.)

(As the starting emine compounds (a piperidine compound, a piperazine compound, etc.), those synthesized by the mothods of Reference Examples 15-1 to 15-11 mentioned below, or known methods or combined methods thereof were used.) Reference Examples 12-97

(1) A mixture comprising 4.5 g of trans-4-(tert-butoxycarbonylamino)cyclohexanacarboxylic acid, 2.29 g of thiomorpholine, 3.90 g of 1-(3-dimethylaminopropyl)-3-eitylaerbodimide, 2.74 g of 1-hydroxybenzotriazol and 30 ml of N.N-dimethylformamide was stirred at room temperature for 4 hours.

The reaction mixture was made bast by adding an aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was suspended in discopropyl either and pracipitates were collected by filtration to obtain N-tert-butoxycarbonyl-trans-4-(4-thiomorpholinylcarbonyl)cy-clohexylamine.

(2) To 50 ml of a chloroform solution containing 5.4 g of the compound obtained in the above (1) was added 8.9 g of 75%-m-chloroporbonzolc acid under ce-cooling, and the mixture was slirred at room lemperature for 1 hour. The reaction mixture was made basic by adding an equeous sodium hydrogenactroenate solution, and extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium suffate, and then, the solvent was removed under reduced pressure. The residue was suspended in disopropyl ether, and precipitates were collected by filtration.

[0170] Then, this compound was suspended in 25 mL of dioxane, 4N hydrochloric acid-dioxane solution (25 mL) was added thereto, and the mixture was stirred for 16 hours. Ether was added to the reaction mixture and procipitates were collected by filtration and dissolved in water. The solution was made basic by adding potassium carbonate, and extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was removed uncer reduced pressure. The residue was suspended in disopropyl ether end precipitates were collected by filtration to obtain trans-4-(1,1-dioxo-4-thiomorpholinyloarbonyloyclobexylamine (Reference Example 12-97 in Table 3).

Reference Examples 13-1 to 13-7

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[0171] To 50 ml of a methylene chloride suspension containing 5.07 g of trane-4-(benzyloxycarbonylamino)cyclohexanezarboxylic acid were added 4.0 ml of thionyl chloride and 0.3 ml of N,N-dimethylformamide and the mixture was stirred at room temperature for 1 hour.

[0172] The reaction mixture was concentrated under reduced pressure and 500 mg of the residual solid was added to 8 ml of an lee-cold methylene chloride solution containing 207 mg of 2-aminopyrimidine and 0.4 ml of triethylamine. After stirring at room temporature for 2 hours, water was added to the reaction mixture and the mixture was extracted with chloroform. The axtract was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (solvent: chloroform-methanol (50:11) to obtain 240 mg of N-benzyloxycarbonyl-trans-4/(pyrmidin-2ylamino)carbonyl/cyclohoxylamina

[0173] This compound was applied to deprotection treatment to obtain trans-4-[(pyrimidin-2-ylamino)carbonyl]cyclohexylamine (Reference Example 13-1 in Table 8).

[0174] Also, the compounds of Reference Examples 13-2 to 13-7 in Table 8 were obtained in the same manner as mentioned above by using the corresponding starting materials instead of 2-aminopyrimidine.

[0175] The deprotection was carried out as mentioned below by using hydrogen bromide-acetic acid. That is, the compound was stirred in 3 mile of 30% hydrogen bromide-acetic acid solution at 50°C for 4 hours. 30 mile of discopreyif either was added to the reaction mixture and procipitates were collected by litiration to obtain a hydrobromide of the deprotected compound. This hydrobromide was made into a solution and the solution was saturated with potassium carbonates and extracted with chloroform to obtain a free form.

[0176] Provided that the deprotection of the compound of Reference Example 13-2 was carried out by using palla-diumcarbon as mentioned below. That is, to a methanol-terrahydrofuran suspension of the compound were added 10% palladium-carbon catalyst and ammonium formate, and the mixture was refluxed. The insolubles were removed by filtration and the filtrate was concentrated under reduced pressure.

Reference Examples 13-8 to 13-16

[0177] Under argon atmosphere, a mixture comprising 1.0 g trans 4-(cenzyloxycarbony)tamino)cyclohexanecarbonyl chicráe, 1.92 go f tributylphenyltin, 61 mg of dichlorobis-(triphenylphesphine)pelladium and 10 mL of dioxane was slirred at 110°C for 12 hours. After cooling, the reaction mixture was concentrated by a centrifugal concentrator, and then, the residue was dissolved in tetrahydrofuran and evaporated to dryness with 5 g of silica gel. The resulting residue was purified by silica gel flash chromatography (solvent: ethyl acetate-hexane (1.2) to (1:1) to obtain 883 mg of N-benzyloxycarbonyl-trans-4-benzoylcylonexylamine.

[0178] 870 mg of this compound was stirred with 1.0 g of trimethylsily iodide and 5 m.L of chlorotoru under argon atmosphere at room temperature for 2 hours. Disappearance of the starting material was confirmed by TLC, 0.17 m.L of methanol and 5 m.L of clothyl either were actided to the reaction mixture and the mixture was stirred at room temperature for 3 days. The resulting procipitates were collected by filtration, washed with anhydrous diethyl ether, and dried to obtain 830 mg of trans-4-berroxive/clohex/theirmine (Reference Example 1.3-8 in Table 8).

[0179] Also, the compounds of Reference Examples 13-9 to 13-16 in Table 8 were obtained in the same manner as mentioned above.

Reference Example 13-17

[0180]

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(1) trans-4-Methoxycarbonylcyclohexane-1-carbonyl chloride was obtained from 5 g of trans-4-methoxycarbonylcyclohaxne-1-carboxylic acid and cxalyl chloride. 7.85 g of morpholine was added dropwises to 50 mL of a methylene chloride solution thereof under loe-cooling, and the mixture was stirred for 2 hours. The reaction mixture was poured into an aqueous 10% citric acid solution, extracted with chloridorm, dried over anhydrous magnesium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel filtash column chromatography (solvent: othyl acetate-haxane (1:1) to ethyl acetate-chloroform (1:1)) and crystallized from hexane to chatin 6.49 g of trans-1-methoxycarbonyl-4-(methoxino-polylo-cyclohaxane.

(2) Under argon atmosphere, 10 mL of a tetrahydrofuran solution containing 2.0 g of the compound obtained in the above (1) was added dropwise to 40 mL of a hexane-tetrahydrofuran (8:5) solution containing LDA (tithlum disporpoylamide) (0.024 mol) prepared at the time of using at 7-8°C and the temperature of the mixture was elevated to -30°C over 2 hours, while stifring. The reaction mixture was cooled again to 7-8°C, reacted with 1.46 mL of mixture) (olde, and allowed to stand to 0°C, and then, water was added therent and the mixture was extracted with entry) acetate. The extract was successively washed with an aqueous 10% citic acid solution, water and brine, dried over an invidrous sodium suitate, and then, the solvent was removed under reduce pressure. The residue was purified by aliba golf lash column chromatography (solvent: ethyl acetate-hoxane (1:2) to (1:1)) to obtain 1.47 golf isomeric mixture of 1-methoxycarbonyl-1-methyl-4-(morpholinocarbonyl)cyclohoxara. This mixture was stirred in a mixture comprising 168 mg of sodium hydroxide, 1 mL of ethanol and 1 mL of water at room temperature for 12 hours. The reaction mixture was extracted with dictityl ether, the extract was washed with water, dired over anhydrous sodium sulfate, and then, the solvent was errowed under reduced pressure. The residue was recrystallized from a mixed solvent comprising eightly either-haxane to obtain 592 mg of single isomer of 1-methoxycar-bonyl-1-methyl-4-(morpholinocarbonyl-xedipoxyare.

(3) 648 mg of the compound (single somen) obtained in the above (2) was stirred in a mixture comprising 251 mg of sodium hydroxide, 5 mL of methanol and 10 mL of water at 110°C for 2 hours. After cooling, pH of the reaction mixture was adjusted to 3 by 10% hydroxinoidro aoid, oxtracted three times with chloroform, the extract was drad over anhytorous magnesium sulfate, and then, the solvent was removed undor roduced prossure. 5 mL of a follower solution containing 479 mg of the resulting compound (cerboxylic acid), 550 mg of giphenylphosphoryl acide and 216 mg of benzyl alcohol was stirred under heating for 12 hours. After cooling, an aqueous 10% citric acid solution was added to the reaction mixture, and the toluene layer was separated, washed with brine and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The resulting residue was purified by silics gel flash chromatography (solvent: chlyl acolate-haxane (1:2)) to (1:1) to obtain 387 mg of N-benzyloxycarbonyl-1-methyl-4-(morp-pholinocarbonylicyclioxyliamine.

[0181] This compound was deprotected by treating with trimethylsityl iodide to obtain 1-methyl-4-(morpholinocarbonyl)cyclohoxylamine (Reference Example 13-17 in Table 8).

Reference Examples 13-18 to 13-21

[0182] N-tert-butoxycarobonyl-trans-4-(1-piperazinylcarbonyl)cyclohexylamine was obtained by treating trans-

4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid and piperazine in the same manner as in the above-mentioned Reference Example 11-1.

[0183] Methyl chlorocerbonate was added dropwise to a mixture comprising 400 mg of this compound, 260 mg of triethy/amine and 8 mt. of methylene chloride under ice-cooling, and the mixture was stirred at room temperature overright. The reaction mixture was successively washed with water and brine, dired over anhyfrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was suspended in disopropyl ether and precipitates were collected by filtration to obtain 410 mg N-tert-butoxycarbonyl-trans-4-(4-methoxycarbonyl-1-plperazinylcarbonyl-tyclohavy/amine.

[0184] This compound was deprotected under acidic conditions according to the conventional method and the acidic mixture was returned to basic to obtain trans-4-(4-methoxycarbonyl-1-piperazinylcarbonyl)cyclohoxylamine (Reference Example 13-18 of Table 8).

[0185] Also, the compounds of Reference Examples 13-19 to 13-21 in Table 8 were obtained in the same manner as mentioned above.

15 Reference Example 13-22

[0186] A mixture comprising 623 mg of N-tert-butoxycarbonyl-trans-4-(piperazinocarbonyl)cyclohexylamine, 340 mg of 3.4-dielhoxy-3-cyclobuten-1,2-dione and 5 mi of ethanol was stirred at room temporature for 2.5 days. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (solvent: chloroform-methanol (50-11) and subsequently triturated with ether.

[0187] This compound was deprotected by treating with hydrochioric acid-dioxane to obtain trans-4-[4-(4-ethoxy-1,2-dioxo-3-cyclobuten-3-yl)piperazinylcarbonyllcyclohexylamine (Reference Example 13-22 in Table 8).

Reference Example 13-23

[0188]

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- (1) A mixture comprising 1101 mg of N-benzyloxycarbonyl-piporazina. 1131 mg of 3.4-dibutoxy-3-cyclobutene-1.2-dione and 6 not elational was stirred at room temperature for 25 hours. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica age column chromatography (solvent: chloroform-ethyl accitate (19:1)) to obtain 1570 rng of 1-benzyloxycarbonyl-4-(4-butoxy-1.2-dioxo-3-cyclobuten-3-y)p-(perzait).
- This compound was deprotected by treating with palladium-carbon in the presence of 3 ml of 10% hydrochloric acid under hydrogen atmosphere to obtain 4-(4-butoxy-1,2-dloxy-3-cyclobuten-3-yl) -piperazine.
- (2) The compound obtained in the above (1) was reacted with trans-(4-benzyloxycarbonylamino)cyclohexanecarbonylahioride in methylene chlorides in the presence of thefulylamine to obtain N-benzyloxycarbonyl-trans-4-[4-(4-butoxy-1,2-claixo-3-cyclobuten-3-yhpiperazinocarbonyijcyclohexylamine.
- (3) The compound obtained in the above (2) and dimethylamine hydrochloride were reacted in channol in the presence of triethylamine to obtain N-benzyloxycarbonyl-trans-41-4(-4-dimethylamino-1,2-dioxo-3-cyclobuten-3-yl)piperaziny carbonyl|cyclohexylamino-1. This compound was deprotected by treating with trimethyls|iy| lodidle to obtain trans-41-4(-4-dimethylamino-1.2-dioxo-3-cyclobuten-3-yl)piperazinyl-carbonyl|cyclohexylamine (Reference Example 13-28 in Table 13-2

Reference Example 13-24

[0189] 0.15 ml of triethylamine and 0.07 ml of mothanosulfonyl chloride were added to 10 ml of a tetrahydrofuranmethylene chloride suspension containing 0.31 g of N-benzyloxycarbonyl-trans-4-(5-hydroxylmothy-0-landichly))
actionyllyclothoxylamine under lee-cooling, and the mixture was stirred under the cooling for 1 hour. Water was added
to the reaction mixture and the mixture was extracted with ethyl sociate. After the extract was dried over sodium sulfate,
the solvent was removed under roduced pressure. To the residue were added 5 ml of dimethylformamide and 0.25 ml
of morpholine, and the mixture was stirred at norn temporature overnight. Water was added to the reaction mixture
and the mixture was extracted with ethyl acetate. After the extract was dried over anhydrous sodium sulfate, the solvent
was removed under reduced pressure. The residue was purified by sillica gel chromatography (solvent chlorionmixture) = 100:1). This compound was treated with peliadum-carbon under hydrogen atmosphero to obtain trans4-(16-morpholinemethy-2-isoloidinily-karbony-levelohexy-lamine (Reference Example 13-24 in Table 8).

Reference Examples 13-25 to 13-29

[0190]

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- (1) 20 g of manganese dioxide was added to 120 ml of a chloroform solution containing 4 0 g of N-banzyloxycarbon-yl-trans-4 (6-hydroxymetry-2-isoindoliry/locrbonylloyclohexylamine, and the mixture was stirred at room temperature for 4 hours. Manganese dioxide was removed by filtration through Ceite and the solvent was removed under reduced pressure. The residue was suspended in hoxane-othyl acetate and the crystals were collected by filtration to obtain N-banzyloxycarbonyl-zeloshezyloxyoxyarbonyl-zeloshezyloxyoxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zeloshezyloxyarbonyl-zelos
 - (2) To an aqueous solution containing 3.35 g of silver nitrate were added 2.75 g of the compound obtained in the above (1) and 110 ml of ethanol under loc cooling, and then, an aqueous solution containing 2.81 g of potessium hydroxide was added dropwise thereto. The mixture was stirred under loc-cooling for 1 hour and separated by filtration through Ceilte, and then, the solvent was removed under reduced pressure. To the residue was added 50 ml of an aqueous 1N hydrochion cadd solution and the mixture was extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was suspended in hexane-ether and the crystals were collected by filtration to obtain N-benzyloxycarbonyl-trans-4-(6-cartoxyz-los indoinylogarbonylicycloboxylamine.
 - (3) The compound obtained in the above (2) was used and condonsed with a starting amine compound in the same manner as in Reference Example 11-1, and subsequently treated with palladium-carbon under hydrogen atmosphere to obtain trans-4-((5-dimethylaminocarbonyl-2-isoindolinyl)carbonyl/cyclohexylamine (Reference 13-25 in Table 8).

[0191] Also, the compounds of Reference Examples 13-26 to 13-29 in Table 8 were obtained in the same manner as mentioned above.

Reference Examples 13-30 to 13-33

[0192]

- (1) 2.6 g of tert-burylcarbamete, S. 5 m of triethylstane and 1.15 m of trifluoreacetic acid were added to 25 m of an acetonitrite suspension containing 3.0 g of N-benzyloxycarbonyl-trans-4-(6.5-formyl-2-isoindolinyl)carbonylloy-clohoxylamine (the compound obtained in Reference Example 13-25 (1)), and the mixture was extracted with chloroform. After the extract was dried over anhydrous softlim sulfate, the evolvent was removed under reduced pressure. The residue was suspended in hexane-ethyl acetate and the crystals were collected by filtration to obtain N-benzy-toxycarbonyl-trans-4-(15-ten-buxoxycarbonyl-minomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonyl/eydehoxylaminomethyl-2-isoindolinyl/pachbonylaminomethyl-2-isoin
 - (2) The compound obtained in the above (1) was treated with palladium-carbon under hydrogen atmosphere to obtain trans-4-[6-tent-butoxycarbonylaminomethyl-2-isoindolinyi)carbonyl[cyclohexylamine (Reference Example 13-30 in Table 81.
- 40 (3) The compound obtained in the above (1) was treated with 4N hydrochloric acid-dioxane to obtain N-benzyloxy-carbonyl-trans-4-[(5-aminomethyl-2-isoindolinyl)carbonyl)cyclohexylamine-hydrochloride.
 - (4) 0.25 ml of cyclocropanecarbonyl chloride was added to 5 ml of a methylene chloride-pyridine solution containing 0.5 g of the compound (hydrochicride) obtained in the above (3), and the mixture was silmed at room reherperature for 4 hours. Diluted aqueous hydrochloric acid solution was added to the reaction mixture and the mixture was extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was romoved under reduced pressure. The residue was purified by silica gel chromatography (solvent: chloroform-mothanoi = 50·1) to obtain crystalis. This compound was treated with palladium-carbon under hydrogen atmosphere to obtain trans-4-(6-cyclopropyl-carbonylaminomethy-2-isoindolinylicarbonyllcydohoxylamine (Reference Example 13-31 in Table 8).

[0193] Also, the compounds of Reference Examples 13-32 to 13-33 in Table 8 were obtained in the same manner as mentioned above.

Reference Example 13-34

[0194]

(1) 0.08 g of hydroxylamine hydrochloride and 0.09 g of sodium formate were added to 3 ml of a formic acid solution

containing 0.3 g of N-benzyloxycarboryl-trans-4-(E-formyl-2-lseindolinyl)carboryl[cyclohaxylarinine (the compound obtained in Reference Example 13.25 (1)), and the mixture was refluxed for 3 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl acotate. After the extract was dried over antilydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by NI+ slica gel othormatography (solvent chloroform-othy) acetate = 50.1), and the resulting compound was treated with trimethyslayi lodide to obtain trans-4-(E-cyano-2-isoindolinyl)carboryl[cyclohaxylamine-hydroiddide (Reference Example 13-34 in Table 18).

Reference Examples 13-35 to 13-46

[0195]

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(1) 17.38 g of stannous chloride was added to a hydrated ethanol (120 ml of ethanol + 1.2 ml of water) suspension containing 6.08 g of N-bearyloxycarbonyl-trans-4(6-nitro-1-indoliny)pectonyligycol-benylamine (the compound obtained in the same manner as in Reference Example 13-1 before deprotection), and the mixture was refluxed under argon atmosphere for 4.5 hours. An aqueous 10% sodium hydroxide solution was added to the reaction mixture to adjust pl of the mixture to pl 49 to 10, the mixture was diluted with 300 ml of chloroform and oried over anhydrous magnesium suifate, and then, the insolubles were removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gol column chromatography (solvent: chloroform-ethyl acetate (2:1)) to obtain 4.72 g of N-benzyloxycarbonyl-trans-4-((6-amino-1-indolinyl)carbonylicy-relevanterials.

(2) 0.12 ml of pyridine and 0.104 ml of acetic anhydride were added to 10 ml of a methylene chloride solution containing 396 mg of the compound obtained in the above (1), and the mixture was stirred for 5 hours, 5% hydrochloride sold was added to the reaction mixture and the mixture was extracted with chloroform. The extracted layer was successively washed with water and an aqueous saturated sodium bloarbonate solution and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel column enhomatography (solvent: chloroform-ethyl acetate (1:11)).

This compound was deprotected by treating with palladium-carbon to obtain traps-4-[(6-acetylamino-1-indoli-nyl)carbonyl[cyclchexylamine (Reference Example 13-35 in Table 8).

Also, the compounds of Reference Examples 13-36 to 13-37 in Table 8 were obtained in the same manner as mentioned above

(3) 0.085 mil of methanesulfonyl chloride was added to 10 mil of a pytidine solution containing 400 mg of the compound obtained in the above (1) all room temperature, and the mixture was stirred for 5 hours. The romained pressure, the residue was dissolved in orhorform, washed successively with 5% hydrochloric acid, water and an aqueous saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent: chloroform-ethyl acetate) (21).

This compound was deprotected by treating with palladium-carbon to obtain trans-4-[(6-methy/suifonylamino-1-indolinyl)carbonyl|cyclohexylamine (Reference Example 13-38 in Table 8).

(4) 15 ml of N.N-dimethylformamide solution containing 403 mg of the compound obtained in the above (1), 189 mg of N.N-dimethylgylcine hydrochloride, 243 mg of 1-ethyl-3(-dimethylaminopropyl)-cathodimide hydrochloride, 173 mg of 1-thylcroxybanzotriazole and 0.181 ml of triethylamine in was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, the residue was clissofved in ethyl accisate, successively wished with an aqueous saturated sodium blearbonate solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silicag el column enhamatography (solvent: theloroform-methanol (50:1)).

This compound was deprotected by treating with palladium-carbon to obtain trans-4-{[6-(dimethylamino}-methylcarbonyl-1-indolinyl]carbonyl]cyclohexylamine (Reference Example 13-39 in Table 8).

(5) 0.8 ml of an aqueous 37% formalin solution and 635 mg of sodium triacetoxyborohydride were added to 10 ml of an acetonitrie suspansion containing 402 mg of the compound obtained in the above (1) at room temperature, and the mixture was stirred for 1.5 hours. The reaction mixture was diluted with water and extracted with entry acetate. The extracted layer was washed with water and brine in order, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The reactive was purfied by silica get column chromatography (solvent: holroform-ethyl acetate (2:1)).

This compound was deprotected by treating with palladium-carbon to obtain trans-4-[(6-dimethylamino-1-in-dolinyl)carbonyl]cyclohexylamine (Reference Example 13-40 in Table 8).

(6) The compounds of Reference Examples 13-41 to 13-46 were obtained in the same manner as in the above (1) to (5) except for using N-benzyloxycarbonyl-trans-4-f(5-nitro-1-indellinyl)carbonylicyclohexylamine (the com-

pound obtained in the same manner as in Reference Example 13-1) as a starting material.

Reference Examples 13-47 to 13-52

- [0196] 451 mg of polassium carbonete and 288 mg of 2-(dimethylamino)ethyl chloride hydrochloride ware added to 5 m of a N.N dimethylformamide solution containing 400 mg of N-benzyloxycarbonyl+rans-4-(6-hydroxy-1-indolinyl) carbonyllcyclohexylamine (the compound obtained in the same menner as in Reference Example 13-1), and the mixture was stirred at 50°C for 19 hours. The reaction mixture was concentrated under reduced pressure, and a solution of the residuo in chloroform-was washed with water, died over sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gal column chromatography (solvent: chloroform-methanol (30:11). [0197] 100 mg of 10% pelladium-carbon catalyst and 920 mg of ammonium formate were added to 10 ml of methanol 10 ml of teitahydrofuran suspension containing this compound, and the mixture was refluxed for 17 hours. The Insolubles were removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 281 mg of trans-4-(16-2-dimethylaminochyloxy-1-indolinylicarbonylicylochyxlamino (Reference Example 13-47 in Table 13-4
- 15 [0198] Also, the compounds of Reference Examples 13-48 to 13-52 in Table 8 were obtained in the same manner as mentioned shows.

Reference Examples 14-1 to 14-16

- 20 [199] A mixture comprising 400 mg of cis-4-(tent-butoxycarbonylamino)cycohexanecarboxylia caid, 216 mg of 4-by-droxypiperidine, 244 mg of 1-hydroxybenzotriazole, 686 mg of O-benzotriazol-1-yl-N,N,N,NHAtramethyluroniumhox-arlluorophosphate, 398 µl of N-methylmorpholine and 11 ml of N,N-dimethyllformamide was stirred at room temperature for 14 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl accester. The extract was wastered with an aqueous 10% citic add solution, water and brine, effect over anhydrous sodium sulfate, and then, of 4N hydrochloric acid-dioxane was added thereto, and the mixture was discoved in 6 ml of dioxane, then, 6 ml of 4N hydrochloric acid-dioxane was added thereto, and then mixture was concentrated or 12 hours. The reaction mixture was concentrated, methanol was added to the residue, and the mixture was concentrated under reduced pressure to obtain olse-4(4-hydroxypherdillocarbonythycochboxylamin-hydrochloride, (Reference Examel 14-1 his file 6).
 - 10 [200] Also, the compounds of Examples 14-2 to 14-16 in Table 8 were obtained in the same manner as mentioned above, using the corresponding starting materials. (Provided that in case of free compounds, they can be obtained by saturating an aqueous solution of a hydrochloride salt compound with potassium carbonate, and after extracting the solution with chloroform, drying the extract over anhydrous sodium sulfate and removing the solvent under reduced pressure.)

Reference Example 15-1

[9201] To a dimethylformamide (7 ml) solution containing N-(tert-outoxycaroonyl)piperazine (1.0 g) were added potassium carbonate (742 mg) and then bulyl iodide (1.0 g), and the mixture was stirred at room temperature for 15 hours to undergo reaction, thereby obtaining N-iert-buoxycarbonyl-N-bulypiperazine. This compound was acid-treated with hydrochloric acid to obtain N-burylpiperazine-dihydrochloride.

[0202] Also, N-isopropylpiperazine-dihydrochloride was obtained in the same manner as mentioned above.

Reference Example 15-2

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[2023] Dimethylamine hydrochloride (430 mg) was added to a methylene chloride (10 ml) solution containing 4-(tertbutoxycarbonyl)piperidone (1.0 g), and under lee-cooling, titethylamine (0.84 ml) and triscelexycorohydride (1.17 g) were further added thordo, and the mixture was stirred at room temperature for 3 hours to undergo reaction, thereby obtaining N-tert-butoxycarbonyl-4-dimethylaminopleridine. This compound was acid-treated with hydrochloric acid to ostain 4-dimethylaminopleridine dihydrochlorid.

Reference Example 15-3

[0204] Sodium triacotoxyborohydride (10.51 g) was added to a methylene chloride (50 ml) solution containing Nformylpiperazine (5.05 g) and cyclohexanecaroxysleldshyde (7.50 g) under co-cooling, and the mixture was stirred at room temperature for 18 hours to undergo reaction, thereby obtaining 1-formyl-4-cyclohexylmethylpiperazine, which was then acid-treated with hydrochloric acid to obtain 1-(cyclohexylmethylpiperazine-hydrochloride.

Reference Example 15-4

[2025] 60% Sodium hydride (0.232.g) was gradually added to a tetralydrofuran (4.5 mt) solution containing 1-tert-butoxycarbonyl-4-hydroxypiperidine (0.900 g) and 2-chloropyrimidine (0.686 g), and 2 hours later, dimethyl sulfoxide (1.0 mt) was added thereto, and the mixture was stirred at room temperature for 1 day to undergo reaction, thereby obtaining 1-tert-butoxycarbonyl-4-(2-pyrimidinyloxypiperidine-hydrochloride

[0206] Also, the following compounds were obtained in the same manner as mentioned above.

- 4-(5-Cyano-2-pyridyloxy)piperidine-hydrochloride
 - 4-(5-Bromo-2-pyrimidinyloxy)piperidine-hydrochloride
 - 4-(p-Nitrophenoxy)piperidine-hydrochloride

Reference Example 15-5

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[0207] A mxture comprising N-(tort-butoxycarbony)piperidine-4-carboxylic acid (700 mg), morpholine (319 μL), 1-cthyl-3-(3-dimensional morpholine) post-post-piperidine-4-carboxylic acid (700 mg), morpholine) (319 μL), 1-cthyl-3-(3-dimensional morpholine) (405 mg), and N-(465 mg), and

[0208] Also, the following compounds were obtained in the same manner as mentioned above.

- 4-(Diethylaminocarbonyl)piperidine-hydrochloride
- 4-(N-methyl -N-benzylaminocarbonyl)piperidine-hydrochloride
- 4 (p-Chlorophenylaminocarbonyl)piperidine-hydrochloride

Reference Example 15-6

[2029] A mixture comprising 4-amino-1-(Ient-butoxycerboryl)-piperidine (700 mg), benzois acid (512 mg), 1-sthyl-3-(3-dimethylaminopropyl)-acobdimide (864 mg), 1-hydroxybenzotratize) (657 mg) and NN-41methylformamile (10 ml) was stirred at room temperature for 16 hours to undergo reaction, and the resulting compound was acid-treated with hydrochioris acid to obtain 4-the protyemathylobioeridine - hydrochloridis.

[0210] Also, the following compounds were obtained in the same manner as mentioned above.

- 4-(2-Pyridylcarbonylamino)piperidine-hydrochloride
- 4-(Cyclohexylcarbonylamino)piperidine-hydrochloride

Reference Example 15-7

[0211] An acetonitrile (7 mi) solution containing N-(tert-butoxycarboryl)piperazine (700 mg), N-methyl-N-phenylcarbamoyl chloride (700 mg) and triethylamine (1.05 ml.) was stirred at room temperature for 15 hours to undergo reaction, and the resulting compound was acid-treated with hydrochloric acid to obtain 1-(N-methyl-N-phenylaminocarboryl) piperazina-hydrochloride.

Reference Example 15-8

[0212] Methanesul'onyl chloride (3.65 ml) was added to a methylene chloride (50 ml) solution containing N-formylplperazine (5.08 g) and triethylamine (6.65 ml) under ice-cooling, and the mixture was stirred at room temperature for 18 hours to undergo reaction, thereby obtaining 1-formyl-4-methanesulfonylpiperazine. This compound was acid-draated with hydrochloric acid to obtain 1-methanesulfonylpiperazine-hydrochloride. Also, 1-(phenylsulfonylpiperazine-hydrochloride was ocialmed in the same manner as mentioned above by using the corresponding starting material.

Reference Example 15-9

[0213] 0.84 ml of triethylamino and 0.37 ml of methanesullonyl etheride were added to 10 ml of a tetrahydrofluran solution containing 0.99 g of 2-tert-butoxycarbonyl-5-(hydroxylmethyl)isoindoline under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. After the extract was dried over socium sulfate, the solvent was removed under reduced pressure. The residue were added 20 ml of ethanol and 1.02 ml of discoorovolethylamine, and the mixture was refluxed for 30 ml.

minutes. The reaction mixture was concentrated under reduced pressure, and aftyl acetate and an aqueous 5% hydrochoice acid solution were added to the residue, followed by the extraction. After the extract was dried over sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (solvent hexane-ethyl scatete – 4:1) to obtain an oily product. This oily product was dissolved in 5 mil of dioxane, then, 8 mil of 4th hydrochiora celd-doxane was added thereto, and the mixture was sistered at room temperature. The precipitates precipitated by addition of 20 mil of either were collected by filtration and washed with either to obtain 5-deboxymethylisionfoldine-hydrochloride.

[0214] Also, the following compounds were obtained in the same manner as mentioned above.

- 5-(Methoxymethyl)isoindoline-hydrochioride
 - 5-(Isopropyloxymethyl)isoindoline-hydrochloride

Reference Example 15-10

³ [0215] 0.85 ml of triethylamine and 0.35 ml of methyl chloroformate were added to 8 ml of a methylame chloride solution containing 0.72 g of 5-amino-2-tert-butoxycarbon-ylisoindollne, and the mixture was stirred at room temperature for 5 hours. Water was added to the reaction mixture and the mixture was catracted with ethyl accistae. After the extract was dried over annydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by silica god chromotography (solvent: chloroform-ethyl accistae 2-1) to obtain an oil. This cill was diseoved in 5 ml of dioxane, then, 8 ml of 4N hydrochloric acid-dioxane was added thereto, and the mixture was stirred at room temperature. The precipitates precipitated by addition of 20 ml of ether were collected by filtration and washed with other to obtain 8-firethoxycarbonylaminolise-indoline-hydrochlorido.

[0216] Also, the following compounds were obtained in the same manner as mentioned above.

25 5-(Acetylamino)isoindoline-hydrochloride

Reference Example 15-11

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[0217] 2-tert-Butoxycarbonyl-5-aminolsoindoline (the compound obtained in the same manner as in WO 00/23428) and dimethylglycine were used as starting materials and reacted in the same manner as in Reference Example 11-1 to obtain 5-(dimethylaminomethylcarbonylamino)isoindoline.

[0218] In the following Table 1a to Table 1d and Table 2 to Table 8, chemical structures and physical properties of the compounds of the above Examples and Reference Examples are shown. (In Tables, "Me" represents a methyl group Also, in Tables, MS APCI (m/z) represents mass spectrometric value (atmospheric pressure chemical ionization mass spectrum).)

Table la

Table la							
	R^2-X H N N						
Exam- ple No.	R ² -X-	R¹	Salt	Physical properties, etc.			
1a-1	02N-_N-H	Н	2HC1	Colorless powder MS·APCI (m/z): 373 [M+H]+			
1a-2	N H	H	2HC1	Brownish powder MS-AFCI (m/z): 328 [M+H]+			
1a-3	NC — H	Н	HC1	Colorless powder MS-APCI (m/z): 353 [M+H]+			
1a-4	F N H	H	2HC1	Colorless powder MS APCI (m/z): 396 [M+H]+			
1a-5	CN NW.	Н	2HC1	Colorless powder MS·APCI(m/z): 353 [M+H]+			
1a-6	NO ₂	Н	2HC1	Yellowish powder MS·APCI(m/z): 373 [M+H]+			
1a-7	N H	Н	2HC1	Colorless powder MS APCI (m/z): 329 [M+H]+			
1a-8	Br-_N''	Н	2HC1	Colorless powder MS·APCI (m/z): 407, 409 [M+H]+			
1a-9	S-N-N-W	Н	2HC1	Pale yellowish powder MS·APCI (m/z): 375 [M+H]+			
1a-10	$CI \leftarrow N \longrightarrow N^{W}$	Н	2HC1	Colorless powder MS:APCI(m/z): 363 (M+H)+			

Table la (continued)

	table la (continued)						
R ² -X-NC							
Example No.	R²-X-	R1	Salt	Physical properties, etc.			
la-11	N HILL	Н	2HC1	Colorless powder MS·APCI(m/2): 329 [M+H]+			
1a-12	N H	Н	HC1	Pale brownish powder MS APCI (m/z): 334 [M+H]+			
1a-13	O ₂ N-\bigcap_N^{\text{Int.}}	Н	HC1	Colorless powder MS APCI(m/z): 372 [M+H]			
1a-14	F F No	Н	HC1	Colorless powder MS APCI(m/z): 440 [M+H]			
la-15	CH ₃ N ^W ··· NO ₂	H	HC1	Colorless powder MS APCI(m/z): 402 [M+H]			
1a-16	CI N N	н	2HC1	Purified powder MS APCI(m/z): 364,362			
1a-17	N H N N	Н	2HC1	Purified powder MS APCI(m/z): 364,362			
1a-18		н	2HC1	Purified powder MS APCI(m/z): 364,362			
1a-19	CI N.	Н	2HC1	Purified powder MS APCI(m/z): 365,363			

Table la (continued)

rable la (continued)						
	R ² -X-NNC					
Example No.	R ² -X-	R1	Salt	Physical properties, etc.		
1a-20	F N N	H	2HC1	Purified powder MS·APCI(m/z): 397		
1a-21	H ₃ C N N	H	2HC1	Purified powder MS·APCI(m/z): 357		
1a-22	N N N	н	2HC1	Purified powder MS APCI(m/2): 354		
1a-23	N N N	Н	2HC1	Purified powder MS-APCI(m/z): 354		
1a-24	CI ZH	н	2HC1	Colorless powder MS APCI(m/z): 378[M+H]+		
1a-25	N:N Hu.	Н	2HC1	Purified powder MS APCI(m/2): 329		
1a-26	NO ₂	Н	HC1	Brownish powder MS·APCI(m/2): 389[M+H]		
1a-27	H ₃ C-S	Н	2HCl	Colorless powder MS·APCI(m/z): 375[M+H]+		

Table la (continued)

Table 1a (Continued)						
	R ² -X-NC					
Example No.	R²−X~	R ¹	Salt	Physical properties, etc.		
1a-28	H ₃ C, S	н	2HC1	Colorless powder MS·APCI(m/z): 447[M+H]+		
1a-29	CI N	H	2HC1	Colorless powder MS APCI(m/z): 448[M+H]+		
1a-30	H,CCO	Н	2HC1	Colorless powder MS-APCI(m/2): 477[M+H]+		
1a-31	H'C O	Н	2HC1	Colorless powder MS·APCI(m/z): 483[M+H]+		
1a-32	H.Z. COOLH	н	2HCl	Colorless powder MS·APCI(m/z): 486(M+H]+		
1a-33	H ₂ C, N, CH ₃	Н	2HC1	Colorless powder MS APCI(m/z): 444[M+H]+		

Table 1a (continued)

Table 10 (Continued)							
	R ² -X-WNC						
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.			
1a-34	H ₂ C O O H	Н	2HCl	Colorless powder MS·APCI(m/z): 470[M+H]+			
1a-35	H,C N	Н	2HC1	Colorless powder MS:APCI(m/z): 485[M+H]+			
1a-36	ON Bu	Н	2HC1	Colorless powder M5·APCI(m/z): 511[M+H]+			
1a-37	H ₂ C. _N . CH ₁	Н	2HC1	Colorless powder MS APCI(m/z): 485[M+H]+			
1a-38	H,C Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	Н	2HC1	Colorless powder MS·AFCI(m/z): 488[M+H]+			
1a-39	H ₃ C-S	H	2HC1	Colorless powder MS·APCI(m/z): 472[M+E]+			

Table la (Continued)

Table 1a (Continued)						
	R ² -X-NC					
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.		
1a-40	H ₃ C N N N	Н	2HC1	Colorless powder MS·APCI(m/z): 446[M+H]+		
1a-41		Н	2HC1	Colorless powder MS·APCI(m/z): 518[M+H]+		
1a-42		Н	2HC1	Purified powder MS APCI(m/z): 405		
1a-43	N - N - N - N - N - N - N - N - N - N -	H	2HC1	Colorless powder MS APCI(m/z): 395[M+H]+		
1a-44	H ₃ C NO ₂	Н	2HC1	Purified powder MS APCI(m/z): 386		
1a-45	NO ₂	Н	2HC1	Purified powder MS APCI(m/z): 372		
1a-46	F CN N	Н	2HC1	Purified powder MS-APCI(m/z): 370		
1a-47	F CN	н	2HCl	Purified powder MS-APCI(m/z): 370		

Table la (Continued)

Table 1a (Continued)						
	R ² -X-NC					
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.		
1a-48	F CN H	Н	2HC1	Purified powder MS·APCI(m/z): 420		
1a-49	H ₂ N CN H	Н	3HC1	Purified powder MS APCI(m/z): 367		
1a-50	P NC	Н	2HC1	Purified powder MS·APCI(m/z): 370		
1a-51	CY _N	н	2HC1	Colorless powder MS APCI (m/z): 352[M+H]		
1a-52,	FULL	Н	2HC1	Colorless powder MS·APCI(m/z): 370(M+H]		
1a-53	Br CN	H	2HC1	Colorless powder MS APCI (m/z): 432,430[M+H]		
1a-54	H ₂ C O ON H	н	2HC1	Colorless powder MS·APCI(m/z): 382[M+H]		
1a-55	N H	Н	2HC1	Colorless powder MS·APCI(m/z): 384[M+H]+		
1a-56	$N_{N_{m}}$	Н	2HC1	Colorless powder MS·APCI(m/z): 368[M+H]+		

Table 1a (continued)

	R^2-X-		R ¹ H N	NC NC
Exam- ple No.	R2-X-	R ¹	Salt	Physical properties, etc.
1a-57	T _N T _N	H	2HC1	Colorless powder MS·APCI(m/z):413[M+H]+
1a-58	N N N N N N N N N N N N N N N N N N N	Н	2HC1	Colorless powder MS·APCI(m/z):419[M+H]+
la-59.	Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	Н	2HC1	Colorless powder MS APCI (m/z): 453 [M+H]+
1a-60	O_2N N N N	H	2HC1	Colorless powder MS·APCI(m/z):373[M+H]+
la-61	NC —NH	H	2HC1	Colorless powder MS·APCI(m/z): 353
1a-62	N H N H	H	2HCl	Pale yellowish powder MS·APCI(m/z): 353 [M+H]+
1a-63	NO ₂	Н	2HC1	Pale brownish powder MS APCI(m/z): 373 [M+H]+
la-64	√ N N N N N N N N N N N N N N N N N N	Н	2HCl	Colorless powder MS APCI(m/z): 329 [M+H]+
1a-65	Br N N	Н	2HC1	Pale yellowish powder MS·APCI(m/z): 409 [M+H]+

Table 1a (Continued)

	R^2-X						
<u></u>			γ	NC			
Exam- ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.			
1a-66	S-W-N-W-W	H	2HC1	Pale yellowish powder MS-APCI(m/z):-375 [M+H]+			
1a-67	N Hum.	Me	2HC1	Colorless powder MS-APCI(m/z): 343 [M+H]+			
1a-68	O5N-{\rightarrow} Har.	Me	2HC1	Pale yellowish powder MS·APCI(m/z): 387[M+H]+			
1a-69	NO3	Me	2HCl	Yellowish powder MS-APCI(m/z): 387[M+H]+			
1a-70	NC-{\rightarrow}Netr	Me	2HC1	Colorless powder MS·APCI(m/z): 367[M+H]+			
1a-71	N Hum.	Me	2HC1	Colorless powder MS-APCI(m/z): 367(M+H)+			
1a-72	N=N-N-	Me	2HCl	Brownish powder MS APCI(m/z): 343 [M+H]+			
1a-73	0 ₂ N-{N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-	Me	2HC1	Pale yellowish powder MS·APCI(m/z): 387[M+H]+			
1a-74	NO ₂	Me	2HC1	Yellowish powder MS·APCI(m/z): 387[M+H]+			
1a-75	NC NH H	Me	2HC1	Colorless powder MS APCI(m/z); 367[M+H]+			

Table la (Continued)

	R ² X		R ¹ H N	O NC
Exam- ple No.	R ² -X-	R1	Salt	Physical properties, etc.
1a-76	CN CN	Me	2HC1	Colorless powder MS·APCI(m/z): 367[M+H]+
1a-77	S N H	CH ₂ OH	2HC1	Pale yellowish powder MS·APCI(m/z): 405[M+H]+
1a-78	NO2 Num	CH ₂ OH	2HC1	Pale yellowish powder MS APCI(m/z): 403[M+H]+
la-79	CN Nur.	СН₂ОН	2HC1	Colorless powder MS APCI(m/z): 383[M+H]+
la-80	O ₂ N N H	CH ₂ OH	2HC1	Pale yellowish powder MS APCI(m/z): 403[M+H]+
1a-81	NC-N-H	CH ₂ OH	2HC1	Colorless powder MS·APCI(m/z): 383[M+H]+
la-82	NC-NH H	CH ₂ OH	2HC1	Colorless powder MS APCI(m/z): 383(M+H)+
1a-83	CN NH	CH ⁵ OH	2HC1	Pale yellowish powder MS·APCI(m/z): 383[M+H]+
la-84	. O ₂ N- N H	CH₂OH	2HCl	Pale yellowish powder MS·APCI(m/z): 403[M+H]+

Table la (Continued)

R ² -X-NC					
Exam- ple No.	R²-X-	R ¹	Salt	Physical properties, etc.	
1a-85	NO ₂	CH ₂ OH	2HCl	Pale yellowish powder MS·APCI(m/z): 403[M+H]+	
1a-86	N CH3	н	2HC1	Purified powder MS·APCI(m/z): 343 [M+H]+	
1a-87	Br N CH ₃	H	2HC1	Purified powder MS APCI(m/z): 421 [M+H]+	
1a-88	N CH3	Н	2HCl	Purified powder MS·APCI(m/z): 343 [M+H]+	
1a-89	NC-NCH3	Н	2HCl	Purified powder MS·APCI(m/z): 367 [M+H]+	

Table 1b

	R ¹							
	R^2-X							
NC NC								
Example No.	R ² -X-	R¹	Salt	Physical properties, etc.				
1b-1	O ₂ N O'III	н	HC1	Colorless powder MS·APCI(m/z): 374[M+H]+				
1b-2	NC-{\bigce_N}Offi	Н	HCl	Colorless crystal Gradually decomposed around at melting point: 233°C MS-APCI(m/z): 354[M+H]+				
1b-3	F NOW	Н	HC1	Colorless powder MS·APCI(m/z): 397[M+H]+				
1b-4	NO ₂	Н	HC1	Pale yellowish powder MS APCI(m/z): 374[M+H]+				
1b-5	NH ₂	н	2HCl	Colorless powder MS·APCI(m/z): 344[M+H]+				
1b-6	Br NOIM.	Н	HCT	Colorless powder MS APCI(m/z): 410[M+H]+				
1b-7	CI—NON,	Н	HCl Free form	Colorless powder MS·APCI(m/z): 364[M+H]+ Colorless crystal Melting point: 129-130°C(decomposed)				
1b-8	CH ₃ S N Ohn	Н	HC1	Pale yellowish powder MS·APCI(m/z): 376[M+H]+				
1b-9	$CH_3O \stackrel{N}{ \swarrow} O^{N^{r'}}$,H	HC1	Colorless MS-APCI(m/z): 360[M+H]+				
1b-10		H	HC1	Colorless powder MS APCI(m/z): 436[M+H]+				

Table 1b (Continued)

				····			
	R ² -X-NONC						
Exam- ple No.	R2-X	R1	Salt	Physical properties, etc.			
1b-11	C N OH.	Н	HC1	Colorless powder MS APCI(m/z): 396[M+H]+			
1b-12	N Own.	Н	HC1	Colorless powder MS APCI (m/z): 330 [M+H]+			
1b-13	0 ₂ N-\	н	HC1	Pale yellowish powder MS APCI (m/z): 373[M+H]+			
1b-14	N Om.	Н	HC1	Purified powder MS·APCI(m/z): 330(M+H]+			
1b-15	CN Om.	н	HC1	Purified powder MS·APCI(m/z): 354[M+H]+			
1b-16	CI N OHI.	H	2HC1	Purified powder MS ·APCI (m/z): 365,363			
1b-17	N CI	H	2HC1	Purified powder MS APCI (m/z): 365,363			
1b-18	CH ₃	Н	2HC1	Purified powder MS·APCI(m/z): 359			
1b-19	N Om.	H	2HC1	Purified powder MS·APCI(m/z): 329			
1b-20	CI N On.	H	2HC1	Purified powder MS APCI(m/z): 365,363			

Table 1b (Continued)

	R^2-X					
Exam- ple No.	R²-X-	R ¹	Salt	Physical properties, etc.		
1b-21	H ₃ C _* O N Om.	Н	2HC1	Purified powder MS·APCI(m/z): 359		
1b-22	N N	Н	HC1	Colorless powder MS ·APCI (m/z): 330 [M+H]+		
1b-23	CI N OW.	н	HC1	Purified powder MS APCI(m/z): 366,364		
1b-24	N CM	н	HC1	Purified powder MS-APCI(m/z): 355		
1b-25	H ₃ C-S	н	HCl	Colorless powder MS APCI (m/z): 376 [M+H]+		
1b-26	F N OW.	Н	HC1	Purified powder MS-APCI(m/z): 398		
1b-27	Hic N Own.	Н	HC1	Purified powder MS-APCI(m/z): 358		
1b-28	N CI	н	HC1	Purified powder MS·APCI(m/z): 356, 364		
1b-29	CI N ₂ OIII.	Н	HC1	Purified powder MS APCI(m/z): 366, 364		
1b-30	N. N. OHIV.	н	HC1	Purified powder MS·APCI(m/z): 330		

Table 1b (Continued)

	R ² -X-NC					
Exam- ple No.	R2-X-	R1	Salt	Physical properties, etc.		
1b-31	H ₁ C N O W	н	2HC1	Purified powder MS APCI(m/z): 456		
1b-32	NO ₂	Н	HC1	Purified powder MS·APCI(m/z): 373		
1b-33	CN CN	Н	HC1	Colorless powder MS·APCI(m/z):353[M+H]		
1b-34	F CN	H	HCl	Colorless powder MS·APCI(m/z): 371(M+H)+		
1b-35	CN Om.	Н	HC1	Colorless powder MS APCI(m/z): 371[M+H]+		
1b-36	F CN	Н	HC1	Colorless powder MS·APCI(m/z): 421(M+H]+		
1b-37	NC F	Н	HC1	Colorless powder MS APCI (m/z): 371 [M+H]+		
1b-38	F CN	Н	HC1	Colorless powder MS·APCI(m/z): 371[M+H]+		
1b-39	H ₃ C CN	Н	HC1	Colorless powder MS APCI(m/z):367[M+H]		

Table 1b (Continued)

	R' N						
	R^2-X						
			1	NC NC			
Exam- ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.			
1b-40	F CN	Н	HC1	Pale brownish powder MS·APCI(m/z):371(M+H)			
1b-41	Br CN	H	HC1	Colorless powder MS·APCI(m/z): 433,431[M+H]			
1b-42	H ₃ C ₁₀ C _N	H	HC1	Colorless powder MS·APCI(m/z):383[M+H]			
1b-43	CI CN Om.	н	HC1	Colorless powder MS·APCI (m/z):387[M+H]			
1b-44	Br CN	H	HC1	Colorless powder MS:APCI(m/z): 433, 431(M+H)			
1b-45	Br. N On.	H	HC1	Purified powder MS-APCI(m/z): 492, 490			
1b-46	O _N	н	HC1	Purified powder MS·APCI(m/z): 406			
1b-47	CI _N Our	H	HC1	Purified powder MS·APCI(m/z): 379			
1b-48	S N OM.	H	HC1	Colorless powder MS APCI(m/z): 385(M+H)+			
1b-49	H ₃ C O O	Н	HC1	Purified powder MS·APCI(m/z): 448			

Table 1b (Continued)

	R ¹ O							
	R ² -X-NC							
Exam- ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.				
1b-50	H ₃ C N CH ₃		2HC1	Purified powder MS APCI(m/z): 445				
1b-51	H ₁ C NH	H	2HC1	Purified powder MS APCI(m/z): 431				
1b-52	C)	н	2HC1	Purified powder MS APCI(m/z): 487				
1b-53	N N N	н	2HC1	Purified powder MS APCI(m/z): 471				
1b-54	H ₁ N N H ₁ C	H	2HC1	Purified powder MS APCI(m/z): 417				
1b-55	H ₃ C _N -CH ₃ H ₃ C _N -CH ₃ H ₃ C _N -CH ₃	Н	2HC1	Purified powder MS·APCI(m/z): 444				
1b-56	H ₂ C, N CH,	Н	2HCl	Purified powder MS-APCI(m/z): 486				

Table 1b (Continued)

	R^2-X H N N					
Exam- ple No.	R2-X-	\mathbb{R}^1	Salt	Physical properties, etc.		
1b-57	H ₃ C _N CH ₃	н	2HCl	Purified powder MS-APCI(m/z): 470		
1b-58	0 ₂ N-(н	HC1	Colorless powder MS·APCI(m/z): 374 [M+H]+		
1b-59	NC-	н	HC1	Colorless powder MS APCI(m/z): 354 [M+H]+		
16-60	FF No	н	HC1	Colorless powder MS APCI(m/z): 397 [M+H]+		
1b-61	CN CN	н	HC1	Colorless powder MS·APCI(m/z): 354 [M+H]+		
1b-62	$Br \leftarrow N O$	Н	HCl	Colorless powder MS APCI(m/z): 408 [M+H]+		
1b-63	S N O	н	HC1	Yellowish powder MS·APCI(m/2): 376 [M+H]+		
1b-64	~o~	H	HC1	Colorless powder MS APCI(m/z): 330 [M+H]+		

Table 1b (Continued)

	R ² -X-N-NC						
Exam- ple No.	R2-X-	R1	Salt	Physical properties, etc.			
1b-65	NO ₂	Me	HC1	Purified powder MS APCI(m/z): 388[M+H]+			
1b-66	NC-\(\bigg ^N \)O(\(\hat{\pi}\).	Me	HC1	Purified powder MS APCI(m/z): 368[M+H]+			
1b-67	NO ₂	Me	HC1	Purified powder MS APCI (m/z): 388 [M+H]+			
1b-68	NC-_N-O	Me	HC1	Purified powder MS APCI(m/z): 368[M+H]+			
1b-69	02N-_N	Me	HCl	Purified powder MS APCI(m/z): 388[M+H]+			
1b-70	Br N O	Me	HC1	Purified powder MS APCI(m/z): 424[M+H]+			
1b-71		Ме	HC1	Purified powder MS-APCI(m/2): 386[M+H]+			

Table 1c

	R ² -X-NC						
Exam- ple No.	R²-X-	R ¹	Salt	Physical properties, etc.			
1c-1	N H	Н	2HC1	Colorless powder MS·APCI(m/z): 356[M+H]+			
1c-2	— H	н	HC1	Colorless powder MS APCI(m/z): 361 [M+H]			
1c-3	N-N-N Jun.	Н	HC1	Purified powder MS·APCI(m/z): 362			
1c-4	○ -1, ym.	H	HC1	Colorless powder MS·APCI(m/z): 355[M+H]+			
1c-5	O CH3	H	HC1	Colorless powder MS·APCI(m/z): 375 [M+H]			
1c-6	CH ₃	H	HC1	Colorless powder MS·APCI(m/z): 383[M+H]+			
1c-7	CH ₃	H	2HC1	Purified powder MS·APCI(m/z): 404			
1c-8	ÇH,	Н	2HC1	Colorless powder MS APCI(m/z): 398 [M+H]			
1c-9	CH3 CH3	н	HC1	Purified powder MS-APCI(m/z): 427			

Table 1c (Continued)

	R^2-X					
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.		
1c-10	H³C-N Mm.	Н	HC1	Colorless crystal Melting point: 211°C (decomposed) MS·APCI(m/z): 307 [M+H]		
1c-11	H ₃ C CH ₃	н	HC1	Purified powder MS·APCI(m/z): 349		
1c-12	H ₃ C N	н	HC1	Colorless powder MS·APCI(m/z): 377 [M+H]+		
1c-13	H ₃ C N N N N N N N N N N N N N N N N N N N	Н	HC1	Purified powder MS APCI (m/z): 349		
1c-14	H³C N Jun.	Н	HC1	Colorless powder MS·APCI(m/z): 363[M+H]+		
1c-15	H ₃ C N	Н	HC1	Purified powder MS APCI(m/z): 365		
1c-16	H ₃ C N	Н	HC1	Colorless powder MS APCI(m/z): 389 [M+H]+		
1c-17	H ₂ N m	Н	HC1	Pale brownish purified resin state MS·APCI(m/z): 279[M+H]+		
1c-18	H ³ C - N	н .	HC1	Purified powder MS·APCI(m/z): 293[M+H]+		

Table 1c (Continued)

	1					
	R ² -X-WH ON NC					
Exam- ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.		
1c-19	H ₃ C N	н	HC1	Purified powder MS·APCI(m/z): 307[M+H]+		
1c-20	H ₃ C N	Н	HC1	Purified powder MS APCI(m/z): 335(M+H)+		
1c-21	H ₃ C H	Н	HC1	Purified powder MS APCI(m/z): 321(M+H)+		
1c-22	H ₃ C CH ₃ O	Н	HC1	Purified powder MS APCI (m/z): 335(M+H]+		
10-23		Н	HC1	Colorless powder MS·APCI(m/z): 357(M+H]+		
1c-24	CN N	H	HC1	Colorless powder MS·APCI(m/z): 357[M+H]+		
1c-25	H ₂ C H	H	HCl	Colorless powder MS·APCI(m/z): 373[M+H]+		
10-26	N H Jum	н	HC1	Colorless powder MS·APCI(m/z): 362(M+H)+		
1c-27	H ₃ C N N M	Н	HCl	Colorless powder MS:APCI(m/z): 376[M+H]+		
1c-28	N N N N	H	HC1	Pale brownish powder MS·APCI(m/z): 363[M+H]+		
1c-29	CD-Ny.	Н	HC1	Colorless purified powder MS·APCI(m/z): 395 [M+H]+		

Table 1c (Continued)

	Table IC (Continued)						
	R ² -X-NC						
Example No.	R²-X-	R ¹	Salt	Physical properties, etc.			
1c-30	H³C ~ N N N N O	H	HC1	Purified powder MS·APCI(m/z): 321[M+H]+			
1c-31	H ₂ C N	Н	HC1	Purified powder MS-APCI(m/z): 335[M+H]+			
1c-32	H ² C N Min.	н	HC1	Brownish purified resin state MS APCI (m/z): 365 [M+H]+			
1c-33	H ₃ C N	H	HC1	Pale brownish purified powder MS·APCI(m/z): 365[M+H]+			
1c-34	H ₃ C O N	H	HCI	Pale brownish purified resin state MS·APCI(m/z): 379[M+H]+			
10-35	H ₃ C N	Н	HC1	Purified powder MS APCI(m/z): 351			
1c-36	HO N'3C	H	HCl	Purified powder MS·APCI(m/z): 351			
1c-37	H ₃ C. O CH ₃	н	HC1	Colorless purified powder MS APCI (m/z): 365[M+H]+			
1c-38	H,C CH, O CH,	H	HC1	Colorless purified powder MS-APCI(m/z): 407(M+H)+			
1c-39	HO CH ₃	Н	HC1	Colorless purified powder MS-APCI(m/z): 351[M+H]+			

Table 1c (Continued)

			CONTRACTOR STATE			
	R ² -X-NC					
Example No.	R²-X-	\mathbb{R}^{λ}	Salt	Physical properties, etc.		
1c-40	H ₃ C O CH ₃	н	HC1	Colorless purified powder MS·APCI(m/z): 379[M+H]+		
1c-41	CH3	Н	HC1	Colorless purified powder MS·APCI(m/z): 333[M+H]+		
1c-42	H ₃ C	H	2HC1	Purified powder MS-APCI(m/z): 370 [M+H]+		
1c-43	H,C-0	Н	2HC1	Purified powder MS-APCI(m/z): 400 [M+H]+		
1c-44	H,C	н	HC1	Colorless purified powder MS APCI(m/z): 409 [M+H]+		
1c-45	H ₃ C-\	H	HC1	Colorless purified powder MS APCI(m/z): 423 [M+H]+		

Table 1c (Continued)

R^2-X					
Example No.	R²-X-	R¹	Salt	Physical properties, etc.	
1c-46	H ₃ C N	Н	HC1	Purified powder MS-APCI(m/z): 307[M+H]+	
1c-47	H ₃ C N	Н	HC1	Colorless powder MS·APCI(m/z): 335 [M+H]+	
1c-48	NC CANORT	H	HC1	Purified powder MS-APCI(m/z): 479 [M+H]+	
1c-49	O2N OWO !!	Ħ	HC1	Purified powder MS·APCI(m/z): 498 [M+H]+	
1c-50	0,N O O N T	Н	HC1	Purified powder MS·APCI(m/z): 492 [M+H]+	
1c-51	NC THE HICK	н	2HC1	Purified powder MS·APCI(m/z): 492 [M+H]+	
1c~52		н	2HC1	Colorless powder MS·AFCI(m/z): 452 [M+H]+	

Table 1d

	Table 1d						
	R ² -X-NC						
Exam- ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.			
1d-1	ON Jun.	Н	HC1	Colorless powder MS-APCI(m/z): 333 [M+H]+			
1d-2	HO ZN Jun.	н	HC1	Purified powder MS APCI(m/z): 363			
1d-3	H3C-0 > N Jun.	Н	HC1	Purified powder MS·APCI(m/z): 377			
1d-4	Os Jun	H	HC1	Colorless powder MS-APCI(m/z): 361 [M+H]+			
1d-5	N-Jum.	Н	HC1	Colorless powder MS:APCI(m/z): 347 [M+H]+			
1d-6	H ₃ C N N	H	HC1	Colorless powder MS·APCI(m/z): 361 [M+H]+			
1d-7	H ₃ C CH ₃	Н	HC1	Colorless powder MS-APCI(m/z): 375 [M+H]+			
1d-8	H ₃ C N N N	H	HCl	Purified powder MS·APCI(m/z): 403[M+H]+			
1d-9	H ₃ C-O N-W	Н	HC1	Purified powder MS APCI (m/2): 405 [M+H]+			
1d-10	H ₂ N N N	н	free form	Purified powder MS APCI(m/z): 390			

Table 1d (Continued)

	R ² -X-NC						
Exam- ple No.	R2-X-	R ¹	Salt	Physical properties, etc.			
ld-11	H ₂ N N N	Н	HC1	Colorless powder MS APCI(m/z): 390 [M+H]+			
1d-12	H ₃ C N	Н	2HC1	Colorless powder MS-APCI(m/z); 390(M+H)+			
1d-13	H ₃ C N N N N N N N N N N N N N N N N N N N	Н	HC1	Purified powder MS·APCI(m/z): 446 [M+H]+			
1d-14	HN N-	H	2HC1	Colorless powder MS·APCI(m/z): 348 [M+H]+			
1d~15	H ₃ C N N N N N N N N N N N N N N N N N N N	Н	2HC1	Purified powder MS-APCI(m/z): 376			
ld-16	H ₃ C N N	Н	2HC1	Colorless powder MS·APCI(m/z): 390[M+H]+			
1d-17	H ² C N N N N N N N N N N N N N N N N N N N	н	2HC1	Colorless powder MS·APCI(m/2): 404[M+H]+			
1d-18	HO N N THIN	Н	2HC1	Colorless powder MS APCI(m/2): 392[M+H]+			
1d-19	H ₃ C N N	н	HC1	Colorless powder MS-APCI(m/z): 390 [M+H]			
1d-20	H³C N N N	Н	HC1	Purified powder MS·APCI(m/z): 404			

Table 1d (Continued)

	nl ·							
5	R ^I O							
	$R^2-X H$ N N							
10				N				
	Example No.	R²-X-	R1	Salt	Physical properties, etc.			
	1d-21	,,, °, ,	н	HC1	Purified powder MS APCI(m/z): 418			
15		H ₃ C N N			MS APCI (m/z): 418			
	1d-22	H ₃ C	Н	HC1	Colorless powder			
		O No Marin		ĺ				
20		H ₃ C H ₃ C						
	1d-23	0 ~	Ħ	HC1	Purified powder			
		H ₃ C N N N			MS · APCI (m/z): 432			
25		H³C, CH³ , Q						
	1d-24	н₁с 0 /¬¬ ј	H	HC1	Purified powder			
		H _J C N N			MS · APCI (m/z): 432			
30	1d-25		Ħ	HC1	Colorless crystal			
					Gradually decomposed at around Melting point:			
		H,C O N			198°C MS·APCI(m/z): 420			
35					[M+H]+			
	1d-26	H ₃ C-S-N N-M''	н	HC1	Purified powder MS APCI(m/z):			
		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			426[M+H]+			
40	1d-27	H ₃ C/ ₁₀ ,	Н	HC1	Colorless crystal			
		O N-Min			Melting point: 207-211°C			
		H ³ C/II/			MS ·APCI (m/z): 377 [M+H]			
45	1d-28		Н	HC1	Colorless crystal			
		<u> </u>			Melting point: 219°C (decomposed)			
	j	O N-MILL			MS APCI(m/z): 349			
]		<u> </u>	1	ethane	[M+H]+ Coloriess crystal			
50				sulfon-	Melting point:			
L			F	c acid	217-218°C (decomposed)			

Table 1d (Continued)

	R ² X	\bigcirc	R ¹ H N	NC NC
Exam- ple No.	R²-X-	R ¹	Salt	Physical properties, etc.
1d-29	S N N	Н	HC1	Colorless powder MS APCI(m/z): 365 [M+H]+
1d-30	O N N N	Н	HC1	Colorless powder MS APCI(m/z): 397 [M+H]+
1d-31	O ₂ N N Juni	Н	HC1	Pale brownish powder MS APCI(m/z): 426 [M+H]+
1d-32	ON Jun.	н	HC1	Colorless crystal Melting point: 198-200°C(decomposed) MS APCI(m/z): 381 [M+H]
1d-33	SN Jun	H	HC1	Pale yellowish powder MS·APCI(m/z): 381[M+H]+
1d-34	N N Hut	н	2HC1	Colorless crystal Melting point: >300°C MS·APCI(m/z): 382[M+H]+
1d-35	₩ _y	н	HC1	Purified powder MS-APCI(m/z): 395
1d-36	S N Thur.	H	HC1	Furified powder MS·APCI(m/z): 401

Table 1d (Continued)

	R ² -X-NC						
Exam- ple No.	R²-X-	R1	Salt	Physical properties, etc.			
1d-37	O-On-Jun.	Н	HC1	Purified powder MS·APCI(m/z): 423			
1d-38	CS N-Jun.	Н	HC1	Colorless powder MS APCI(m/z): 429 [M+H]+			
1d-39	сн,о-()-()-()-	Н	HC1	Colorless powder MS·APCI(m/z): 451 [M+H]+			
1d-40	_N_N_M	Н	HC1	Purified powder MS·APCI(m/z): 424			
1d-41	CH1 NJW.	Н	2HC1	Colorless powder MS-APCI(m/z): 438 [M+H]			
1d-42	CI-Q-NONJu.	Н	2HC1	Colorless powder MS APCI(m/z): 458 [M+H]			
1d-43	CH10-1-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N	H	2HC1	Purified powder MS·APCI(m/z): 454			
1d-44	~ N N Jun.	Н	2HC1	Purified powder MS·APCI(m/z): 425			
1d-45	CN-N N-Jur.	Н	2HC1	Colorless powder MS APCI(m/z): 426[M+H]+			

Table 1d (Continued)

	Table Id (Concinued)						
	R ² -X-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN						
Exam-	R²-X-	R1	NO Salt	Physical			
ple No.	R-x-	L.		properties, etc.			
1d-46	OG O T	Н	HCl	Colorless powder MS·APCI(m/z): 492[M+H]+			
1d-47	O NO NAME.	Н	2HCl	Purified powder MS·APCI(m/z): 444[M+H]+			
1d-48	O NON Jun.	Н	2HC1	Purified powder MS·APCI(m/z): 438			
1d-49	CH ₃	Н	2HC1	Colorless powder MS APCI(m/z): 466 [M+H]			
1d-50	H ₃ C CH ₃ N N N	H	2HC1	Purified powder MS APCI(m/z): 494			
1d-51	N Jun.	Н	HC1	Purified powder MS APCI(m/z): 437			
1d-52	ENTO NAME.	Н	Maleic acid	Purified powder Melting point: 180-183°C			
1d-53	NC (N CN Juni	н	HC1	Purified powder MS APCI(m/z): 465			
1d-54	B _r N N N N N N N N N N N N N N N N N N N	Н	HCI	Purified powder MS APCI(m/z): 521, 519			

Table 1d (Continued)

	Table 1d (Continued)						
	R ² -X-NC						
Exam- ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.			
1d-55	O'N O ON Jun.	н	HC1	Purified powder MS APCI(m/z): 484			
1d-56	N-Jun-	H	HC1	Purified powder MS·APCI(m/z): 451			
1d-57		H	HCl	Purified powder MS APCI(m/z): 460 [M+H]+			
1d-58	DIN NJM.	н	HC1	Purified powder MS·APCI(m/z): 416			
1d-59	C Z Z Z Z Z	н	HC1	Purified powder MS·APCI(m/z): 458			
1d-60		Н	HC1	Colorless powder MS-APCI(m/z): 452 [M+H]			
1d-61		н	2HC1	Colorless powder MS-APCI(m/z): 453 [M+H]			
1d-62	ST NONT	н	HC1	Colorless powder MS·APCI(m/z): 458 [M+H]			

Table 1d (Continued)

	Table 1d (continued)						
.00	R ² -X-NC						
Exam- ple No.	R2-X-	R1	Salt	Physical properties, etc.			
1d-63	N N N	Н	HC1	Colorless powder MS·APCI(m/z): 455 [M+H]			
1d-64		н	HC1	Colorless powder MS·APCI(m/z): 461 [M+H]+			
1d-65	\$\frac{1}{2} - \times	Н	HCl	Purified powder MS·APCI(m/z): 488[M+H]+			
1d-66		н	HC1	Colorless powder MS-APCI(m/z): 467 [M+H]+			
1d-67		Н	HC1	Purified powder MS·APCI(m/z): 500 [M+H]+			
1d-68		Н	HC1	Colorless powder MS·APCI(m/z): 481 [M+H]+			
1d-69		H	HC1	Purified powder MS·APCI(m/z): 494 [M+H]+			
1d-70		Н	HC1	Colorless powder MS·APCI(m/z): 482 [M+H]+			
1d-71		Н	HC1	Purified powder MS·APCI(m/z): 466 [M+H]+			

Table 1d (Continued)

	Table ta (continued)					
	R ² -X-NC					
Exam- ple No.	R ² -X-	R ^l	Salt	Physical properties, etc.		
1d-72		Н	2HC1	Purified powder MS-APCI(m/z): 467 [M+H]+		
1d-73		H	HC1	Purified powder MS·APCI(m/z): 472 [M+H]+		
1d-74		Н	2HC1	Purified powder MS-APCI(m/z): 514[M+H]+		
1d-75	HO	Н	HCI	Purified powder MS·APCI(m/z): 377		
1d-76	H ₃ C V	H	HC1	Purified powder MS·APCI(m/z): 377		
1d-77		Н	2HC1	Colorless powder MS-APCI (m/z): 484 [M+H]		
1d-78	H ₂ C-N N Jun.	н	HC1	Purified powder MS·APCI(m/z): 376		
1d-79	H ₅ C ~ L ~ Y	н	HCl	Pale yellowish powder MS·APCI(m/z): 420[M+H]+		
1d-80	H,C-N N N	Н	HC1	Colorless powder MS APCI(m/z): 419 [M+H]		

Table 1d (Continued)

	Table 14 (conclinact)							
	R ² -X-NC							
Example No.	R ² -X-	R1	Salt	Physical properties, etc.				
1d-81	H,C~>	Н	HC1	Colorless purified powder MS APCI (m/z): 524 [M+H]+				
1d-82	H ₃ C-O	H	HC1	Colorless purified powder MS·APCI(m/z): 453(M+H]+				
1d-83	H ₃ C-9	Н	HC1	Colorless powder MS APCI (m/z): 411 [M+H]+				
1d-84	H,C X Y	Н	2HC1	Colorless purified powder MS APCI (m/z): 481 [M+H]+				
1d-85	H ₃ C ⁻³ S ^{-N} CC ymr	H	HC1	Colorless purified powder MS·APCI(m/z): 474 [M+H]+				
1d-86	но	н	HC1	Purified powder MS·APCI(m/z): 411[M+H]+				
1d-87	H ³ C _{-O} C N Jun.	H	HC1	Colorless purified powder MS·APCI(m/z): 411[M+H]+				
1d-88	Hic J C N Jun.	Н	HC1	Colorless purified powder MS APCI (m/z): 425(M+H)+				
1d-89	HO TON Y	н	HCl	Colorless powder MS·APCI(m/z): 397[M+H]+				
1d-90	H,N-\$ N	Н	free form	Colorless solid MS·APCI(m/z): 460[M+H]+				
1d-91	H ₃ C-ON JW	н	HC1	Colorless powder MS-APCI(m/z): 425 [M+H]+				

Table 1d (Continued)

	Table 1d (Continued)					
R ² -X-V						
Example No.	R ² -X-	R ^I	NC Salt	Physical properties, etc.		
1d-92	HO N	Н	HC1	Colorless powder MS·APCI(m/z): 397 [M+H]		
1d-93	HN	Н	HCl	Purified powder MS APCI(m/z): 410		
1d-94		H	HC1	Purified powder MS·APCI(m/z): 340 [M+H]		
1d-95	NC C	H	HC1	Purified powder MS-APCI(m/z): 365 [M+H]		
1d-96	CI	Н	HC1	Colorless powder MS·APCI(m/z): 374[M+H]		
1d-97	NO ₂ O	H	HC1	Yellowish powder MS·APCI(m/z): 385(M+H)		
1d-98	H ₃ C CH ₃	H	HC1	Colorless powder MS-APCI(m/z): 382[M+H]		
1d-99		Н	HC1	Purified powder MS-APCI(m/z): 330 [M+H]		

Table 1d (Continued)

	Table 1d (Continued)				
5	×	R ² -X-	R¹ H H N) NC	
10	Example No.	R²-X-	Rl	Salt	Physical properties, etc.
15	1d-100	200	н	HC1	Purified powder MS APCI(m/z): 346 [M+H]
20	1d-101	CIS S	Н	HC1	Colorless powder MS APCI (m/z): 396[M+H]
25	1d-102		Н	2HC1	Colorless powder MS APCI (m/z): 341 [M+H]
	1d-103		Me	HC1	Purified powder MS·APCI(m/z): 363 [M+H]
30	1d-104	H ₂ C-0 N	Н	HC1	Colorless powder MS·APCI(m/z): 406[M+H]
35	1d-105	4,c~~o^h\\	н	HC1	Colorless powder MS·APCI(m/z): 448[M+H]
	1d-106	H,C~OLN N-J	н	HC1	Colorless powder MS·APCI(m/z): 434[M+H]
40	1d-107	O-,0	H	HC1	Colorless powder MS-APCI(m/z): 468(M+H)
45	1d-108	o=\$-\\-\-\-\-\	H	HC1	Pale yellowish powder MS·APCI(m/z): 472 [M+H]
50	1d-109	O N CH ₁	н	HC1	Pale yellowish powder MS APCI(m/z): 471 [M+H]

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Table 1d (Continued)

T	nl						
	R^2-X						
			NO	· • · · · · · · · · · · · · · · · · · ·			
Example No.	R²-X-	R ¹	Salt	Physical properties, etc.			
1d-110	H,C O CON MAN.	Ħ	HC1	Purified powder MS APCI(m/z): 439 [M+H]+			
ld-111	H ₂ C-0 N	Н	HC1	Colorless purified powder MS·APCI(m/z): 425 [M+H]+			
1d-112	H°C 10 1	Н	HC1	Purified powder MS:APCI(m/z): 453 [M+H]+			
ld-113	H,C'OY HOW	H	HCl	Colorless purified powder MS APCI (m/z): 454 [M+H]+			
ld-114	",cT"	н	HC1	Colorless purified powder MS APCI(m/z): 438			
1d-115	and	H	2HC1	Purified powder MS·APCI(m/z): 480 [M+H]+			
ld-116	H,C-V,CH,	н	HCl	Colorless purified powder MS:APCI(m/z): 452 [M+H]+			
1d-117	·	Н	HC1	Colorless purified powder MS APCI(m/z): 424 [M+H]+			
1d-118	HO HIN-E	н	HCl	Colorless purified powder MS·APCI(m/z): 468 [M+H]+			
1d-119	olog	Н	HC1	Colorless purified powder MS APCI(m/z): 478 [M+H]+			
1d-120	0,001	н	HC1	Colorless purified powder MS APCI(m/z): 494 (M+H)+			

Table 1d (Continued)

	R ² -X-NC						
Example No.	R2-X-	R ¹	Salt	Physical properties, etc.			
ld-121	H ₂ N CON	H	2HC1	Colorless purified powder MS APCI(m/z): 410			
1d-122	dimor	H	HC1	Colorless purified powder MS APCI (m/z): 478 [M+H]+			
1d-123	H,C N CON	Н	HC1	Colorless purified powder MS·APCI(m/z): 452[M+H]+			
1d-124	No. S. M. C. M. M.	H	HC1	Colorless purified powder MS·APCI(m/z): 488[M+H]+			
1d-125	NC CONT	H	HC1	Colorless purified powder MS·APCI(m/z): 406 [M+H]+			
ld-126	H ₁ C L _N	H	HC1	Colorless powder MS·APCI(m/z): 438 [M+H]			
1d-127	H,C N 1 5 7	Н	HC1	Colorless powder MS·APCI(m/z): 467 [M+H]			
1d-128	H,C, L, Sh T	H	HC1	Colorless powder MS APCI(m/z): 454 [M+H]			
1d-129	H'C-	н	HC1	Colorless powder MS·APCI(m/z): 474 [M+H]			
1d-130	H ₃ C _N J _B C _N	Н	2HC1	Colorless powder MS·APCI(m/z): 481 [M+H]			

Table 1d (Continued)

R^2-X						
Exam- ple No.	R²-X-	R1	Salt	Physical properties, etc.		
1d-131	H _J C N	Н	SHC1	Colorless powder MS·APCI(m/z): 424 [M+H]		
1d-132	H ₃ C N	Н	HC1	Colorless powder MS APCI(m/z): 438 [M+H]		
1d-133	H ₃ C, N	Н	HC1	Yellow brownishpowder MS·APCI(m/z): 467 [M+H]		
ld-134	H,C of Only	Н	HC1	Colorless powder MS APCI(m/z): 454 [M+H]		
1d-135	H ₃ C ₃ O	н	HC1	Colorless powder MS APCI(m/z): 474 [M+H]		
1d-136	H,C-N	H	2HC1	Pale brownish powder MS:APCI(m/z): 481 [M+H]		
1d-137	H,C, N	Н	2HC1	Colorless powder MS·APCI(m/z): 424 [M+H]		
1d-138	H ₃ C,	H	2HC1	Pale yellowish powder MS APCI(m/z): 468(M+H)+		
1d-139	M.C. COMP	H	HC1	Colorless powder MS·APCI(m/z): 411[M+H]+		
ld-140	H ₃ C N O N	н	HCl	Colorless powder MS·APCI(m/z): 468[M+H]+		
ld-141	H ₃ C-O	Н	HC1	Colorless powder MS·APCI(m/z): 469 [M+H]		

Table 1d (Continued)

	table in (concluded)						
	R ² -X-NC						
Example No.	R2-X-	R¹	Salt	Physical properties, etc.			
1d-142	H,C-N H,C	Н	HC1	Colorless powder MS·APCI(m/z): 468[M+H]+			
1d-143	"'S-ESTIA	Н	HC1	Colorless powder MS·APCI(m/z): 469[M+H]+			
1d-144	но-Си-	Н	HC1	Purified powder MS·APCI(m/z): 363 [M+H]+			
1d-145	~~/	Н	HC1	Colorless powder MS·APCI(m/z): 349 [M+H]+			
ld-146		Н	HC1	Purified powder MS·APCI(m/z): 381 [M+H]+			
ld-147	HO HO	н	HCl	Colorless powder MS APCI(m/z): 425 [M+H]+			
1d-148		Н	2HC1	Colorless powder MS APCI(m/z): 425 [M+H]+			
1d-149		н	2HC1	Colorless resin state MS APCI(m/z): 430 [M+H]+			
1d-150	HO	Н	HC1	Colorless powder MS·APCI(m/z): 439 [M+H]+			

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Table 1d (Continued)

R ² -X-NNC					
Example No.	R2-X-	R ¹	Salt	Physical properties, etc.	
1d-151	CH ₃	Н	2HC1	Purified powder MS·APCI(m/z): 438 [M+H]+	
1d-152		Н	2HC1	Colorless powder MS:APCI(m/z): 438 [M+H]+	

Table 2

	nl						
	R ² -X-\(\sigma\) H O NC						
		,	111				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.			
2-1	NC N N	Me	2HC1	Purified powder MS-APCI(m/z): 366			
2-2	NC NIIII	Me	2HCl	Purified powder MS·APCI(m/z): 366			
2-3	NC — H	Ме	2HC1	Purified powder MS·APCI(m/z): 366			
2-4	NC — Hinn.	Me	2HC1	Purified powder MS·APCI(m/z): 366			
2-5	Nu.	Me	2HC1	Purified powder MS·APCI(m/z): 366			
2-6	H ₃ C ^O	Me	2HC1	Purified powder MS·APCI(m/z): 371			
2-7	F NW	Me	2HC1	Purified powder MS·APCI(m/z): 359			
2-8	○ Nm.	Ме	2HC1	Purified powder MS·APCI(m/z): 347			

Table 3

	R^2-X R^1 H N N							
Exam- ple No.	R²-X-	R ¹	Salt	Physical properties, etc.				
3-1	N H	Н	2HC1	Colorless powder MS·APCI (m/z): 370 [M+H]+				
3-2	CH3 O	Н	2HC1	Colorless powder MS·APCI(m/z): 370 [M+H]+				
3-3	Z N	Н	2HC1	Colorless powder MS·APCI(m/z): 357 [M+H]+				
3-4	N H	Н	2HC1	Resin state MS APCI(m/z): 371 [M+H)+				
3-5	CN I HJW.	н	2HC1	Resin state MS·APCI(m/z): 371 [M+H]+				
3-6	H ² C N H	н	2HC1	Resin state MS·APCI(m/z): 400 [M+H]+				

Table 3 (Continued)

	table 3 (continued)						
	R ² -X-NC						
Example No.	R2-X-	R ¹	Salt	Physical properties, etc.			
3-7	CN Jun.	н	2HC1	Resin state MS·APCI(m/z): 384 [M+H]+			
3-8	H,C-0~H	Н	HC1	Colorless powder MS·APCI(m/z): 337 [M+H]+			
3-9	H ₃ C N N N	н	HC1	Colorless powder MS·APCI(m/z): 335 [M+H]+			
3-10	HO N Jun.	н	HC1	Pale yellowish powder MS·APCI(m/z): 363 [M+H]+			
3-11	H ³ C-N M Mun.	Н	2HC1	Colorless powder MS APCI(m/z): 362 [M+H]+			
3-12	OCH ₃	Н	HC1	Colorless powder MS-APCI(m/z): 455 [M+H]+			

m-41- 4

	Table 4							
	R ² -X-NC							
Exam~ ple No.	R ² -X-	R ¹	Salt	Physical properties, etc.				
4-1	O ₂ N N H	н	2HC1	Pale yellowish powder MS APCI (m/z): 391 [M+H]+				
4-2	_N_N,	н	2HC1	Colorless powder MS APCI(m/z): 346[M+H]+				
4-3	NC NC H	H	2HC1	Pale yellowish powder MS-APCI(m/z): 371 [M+H]+				
4-4	F N H	н	2HC1	Colorless powder MS APCI(m/z): 414[M+H]+				
4-5	⟨N H	н	HC1	Colorless powder Melting point: >300°C MS APCI (m/z): 347 [M+H]+				
4-6	Br—N N	H	2HC1	Colorless powder MS APCI (m/z): 425 427 [M+H]+				
4-7	H ₃ C S N H	H	2HC1	Colorless powder MS·APCI(m/z): 393 [M+H]+				
4-8	$CI \stackrel{N}{\longleftarrow} \stackrel{H}{\stackrel{M}{\longrightarrow}} \stackrel{M}{\stackrel{M}{\longrightarrow}} $	H	2HC1	Colorless powder MS APCI(m/z): 381				
4-9	$\begin{bmatrix} S \\ N \end{bmatrix} \stackrel{N}{\longrightarrow} $	Н	2HC1	Colorless powder MS·APCI(m/z): 352 [M+H]+				
4-10	O_2N N N N	Н	2HC1	Pale yellowish powder MS·APCI(m/z): 391 [M+H]+				
4-11	O_2N O_{II}	Н	HC1	Colorless powder MS·APCI(m/z): 392(M+H]+				

Table 4 (Continued)

	R ² -X-NC					
Exam- ple No.	R ² -X-	R1	Salt	Physical properties, etc.		
4-12	NC NO OHI.	н	HCl	Colorless powder MS APCI(m/z): 372[M+H]+		
4-13	Br NOIN.	Н	HC1	Colorless powder MS·APCI(m/z): 426(M+H)+		
4-14	CI-\(\bigc\) OII.	Н	HC1	Colorless powder MS ·APCI(m/z): 382[M+H]+		
4-15	H ₃ C N S	н	HC1	Colorless powder MS·APCI(m/z): 394[M+H]+		
4~16		Н	HC1	Colorless powder Melting point: 80°C- (Decomposed) MS APCI (m/z): 348 [M+H]+		
4-17		Н	HC1	Colorless powder MS APCI(m/z): 414 [M+H]+		
4-18	0 ₂ N-\(\sigma\)-0 ^{kt'}	Н	HC1	Pale yellowish powder MS·APCI(m/z): 391[M+H]+		
4-19	N= N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N	H	2HC1	Colorless powder MS·APCI(m/z): 374 [M+H]+		
4-20	H ₂ N Mur.	Н	HCl	Colorless purified powder MS·APCI(m/z): 297[M+H]+		
4-21	CH3 H3C N	Н	HC1	Purified powder MS APCI(m/z): 325[M+H]+		
4-22	H ₃ C O N N N N N N N N N N N N N N N N N N	Н	HC1	Colorless purified powder MS·APCI(m/z): 397[M+H]+		

Table 4 (Continued)

	:						
·	R ² -X-NC						
Example No.	R²-X-	Ř1	Salt	Physical properties, etc.			
4-23	H ₃ C	Н	HC1	Colorless powder MS APCI (m/z): 438[M+H]+			
4-24	H³C-O	Н	HC1	Colorless powder MS·APCI(m/z): 423[M+H]+			
4-25	H,c-0	Н	HC1	Colorless purified powder MS APCI (m/z): 471 [M+H]+			
4-26	. Oy Jun.	Н	HC1	Colorless powder MS·APCI(m/z): 367[M+H]+			
4-27	Cy Jun.	Н	HC1	Colorless powder MS APCI(m/z): 351[M+H]+			
4-28		Н	HC1	Colorless powder MS APCI(m/z): 399[M+H]+			
4-29	H ₂ N N	Н	2HC1	Colorless powder MS APCI (m/z): 414 [M+H]+			
4-30	но	Н	HC1	Colorless powder MS·APCI(m/z): 429[M+H]+			
4-31	O ₂ N N	Н	HC1	Colorless powder MS·APCI(m/z): 444[M+H]+			
4-32	H ₁ C-N	Н	HC1	Colorless powder MS·APCI(m/z): 486[M+H]+			

Table 5

	Table 5						
	$R^2-X-\sqrt{\sum_{j=1}^{R}NH_2}$						
Reference Example No.	R ² -X-	R1	Salt	Physical properties, etc.			
3-1	O2N-NAME	Н	Free form	Yellowish crystal Melting point: 156-158°C			
3-2	⟨N H	H	free form	Pale brownish crystal Melting point: 110-122°C			
3-3	NC N H	H	form	Colorless crystal Melting point: 152-154°C			
3-4	F N N	Н	Free form	Pale brownish crystal Melting point: 77-80°C			
3-5	€ Hu.,	H	form	Pale yellowish needle-like crystal Melting point: 107-108°C			
3-6	NO ₂	Н	form	Yellowish needle-like crystal Melting point: 84°C-			
3-7	N H	Н	Free form	Colorless crystal Melting point: 128-129°C			
3-8	Br-CN-Natur	Н	Free form	Colorless crystal Melting point: 140-141°C			
3-9	H ₃ C N N W	Н	Free form	Pale yellowish crystal Melting point: 116-118°C			
3-10	CI—	Н	2HC1	Colorless crystal Melting point: >300°C			
3-11	N H	Н	Free form	Pale yellowish needle-like crystal Melting point: 92-94°C			
3-12	[s-Hw	Н	free form	Brownish crystal Melting point: 120-123°C			

Table 5 (Continued)

	1001	e 5 (continue	1)
Reference Example No.	R ² -X-	R1	Salt	Physical properties, etc.
3-13	CI N MIN.	H	free form	Powder MS·APCI(m/z): 228,226
3-14	N N N	Н	free form	Oil MS ·APCI (m/z): 228,226
3-15	CI N N N	Н	Free form	Oil MS APCI(m/z): 228,226
3-16	N T N T CI	H	free form	Oil
3-17	F N N	H	Free form	Powder MS APCI(m/z): 261
3-18	H ₃ C N N N N	Н	Free form	Oil MS·APCI(m/z): 221
3-19	h L Hu.	Н	free form	Powder MS APCI(m/z): 218
3-20	ENT NAME.	H	Free form	Powder MS APCI (m/z): 218
3-21	H ₅ C ₂ S _N	H	Free form	Yellowish oil MS·APCI(m/z): 239[M+H]+
3-22	H,C N	Н	Free form	Yellowish foam MS·APCI(m/z): 311[M+H]+
3-23	H,C. D. M.	Н	Free form	Yellowish oil MS APCI(m/z): 312[M+H]+
3-24	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Н	Free form	Colorless oil
3-25		H	Free form	Colorless oil

Table 5 (Continued)

Reference Example No.	R²-X-	R ¹	Salt	Physical properties, etc.
3-26	ON Em	Н	Free form	Powder MS·APCI(m/z): 269
3-27		Н	Free form	Yellowish oil MS·APCI(m/z): 259[M+H]+
3-28	H ₃ C NO ₃	Н	Free form	Oil MS·APCI(m/z): 250
3-29	C NO.	Н	Free form	Powder MS·APCI(m/z): 236
3-30	F CN N	Н	form	Powder MS·APCI(m/z): 234
3-31	O Car	Н	Free form	MS APCI(m/z): 234
3-32		Н	Free form	Powder MS-APCI(m/z): 284
3-33	H ² N CN H _m .	н	free form	Powder MS·APCI(m/z): 231
3-34	NC Nym	н	free	Powder MS:APCI(m/z): 234
3-35	CN H	н	form	Pale brownish crystal Melting point: 99-102°C MS APCI(m/z): 216[M+H]
3-36	F CN	Н	Free form	Yellowish resin MS·APCI(m/z): 234[M+H]
3-37	Br. CN	н	Free form	Pale reddish brownish powder MS·APCI(m/2): 296, 294[M+H]
3-38	H1C-O CN	Н	free form	Pale reddish brownish powder MS·APCI(m/z): 246[M+H]

Table 5 (Continued)

5	Reference Example No.	R ¹ -X-Y-	R ²	Salt	Physical properties, etc.
10	3-39		н	Free form	Oil
	3-40	ON 2 Nam	Н	Free form	Oil
15	3-41	O ₂ N-NHIIII	н	Free form	Yellowish crystal Melting point: 135-136.5°C
20	3-42	Cl	H	Free form	Yellowish powder MS·APCI(m/z): 242[M+H]+
25	3-43	F F NO2	H	Free form	Yellowish crystal Melting point: 81.5-83.5°C
	3-44	H ₂ C NO ₂	Ħ	free form	Reddish liquid MS·APCI(m/z): 266 [M+H]
30	3-45	O. Hum.	Н	Free form	Dark reddish powder MS APCI(m/z): 253[M+H]
35	3-46	CI N. N. N.	Н	Free form	Powder MS·APCI(m/z): 229,227
40	3-47		Н	Free form	oil
45	3-48	N.S.N. N.W.	H	Free form	Powder MS·APCI(m/z): 193
50	3-49	Of Jun.	H	Free form	Oil
55	3-50		н	Free form	Colorless oil

Table 5 (Continued)

	Table	J (C	ontinued	17
Reference Example No.	R2-X-	R ¹	Salt	Physical properties, etc.
3-51	H ₂ C. , CH ₃	Н	Free form	Colorless oil
3-52	M ₂ C \ O \ O \ O \ O \ O \ O \ O \ O \ O \	Н	Free form	Colorless oil
3-53	H,C, N	н	Free form	Yellowish oil
3-54		н	Free form	Colorless oil
3-55	N.C. COL	н	free form	Colorless oil
3-56		н	Free form	Yellowish oil
3-57	H,C-S	Н	Free form	Colorless foam
3-58	H ₃ C N N N	н	Free form	Colorless oil
3-59		Н	Free form	Colorless oil

Table 5 (Continued)

			,	0011021140	~_/
5	Reference Example No.	R²-X-	R ¹	Salt	Physical properties, etc.
	4	0 ₂ N-\(\bigce_N - \bigce_H \)	Н	Free form	Pale yellowish solid Melting point: 153-155°C
10	5-1	NO ₂	н	2HCl	Yellowish crystal Melting point: 219-222°C
15	5-2	NC-_NH	H	2HCl'	Colorless powder MS·APCI(m/z): 217 [M+H]+
20	5-3	CN NH	Н	2HC1	Colorless crystal Melting point: 215-218°C
	5-4		H	2HC1	Colorless crystal Melting point: 245-250°C
25	5-5	Br N H	н	2HC1	Colorless crystal Melting point: 303°C
30	5-6	H _J C _S -N-N	н	2HC1	Yellowish crystal Melting point: 234-237°C
	7-1	ZN Hun.	Me	Free form	Colorless crystal Melting point: 121-123°C
35	7-2	0°N-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	Me	Free form	Yellowish crystal Melting point: 164-166°C
40	7-3	NO. THE	Me	Free form	Yellowish crystal Melting point: 40-43°C
	7-4	NC-_NH"	Me	Free form	Pale yellowish crystal Melting point: 147-148°C
45	7-5	∑N N _m .	Me	free form	Colorless crystal Melting point: 111-112°C
50	7-6	0 ₂ N-_N-\\	Me	Free form	Pale brownish crystal Melting point: 121-124°C
55	7-7	NO ₂	Me	Free form	Yellowish crystal Melting point: 58-59°C

Table 5 (Continued)

5	Reference Example No.	R²-X-	R1	Salt	Physical properties, etc.
10	7-8	NC -N	Me	Free form	Colorless crystal Melting point: 182-184°C
	7-9	Z N Z	Me	free form	Pale brownish crystal Melting point: 76-79°C
15	7-10	NO ₂	CH ₂ OH	2HC1	Pale yellowish solid MS·APCI(m/z): 267[M+H]+
20	7-11	CN Nam.	CH₂OH	2HC1	Colorless solid MS·APCI(m/z): 247[M+H]+
25	7-12	O ₂ N — NHW**	СН₂ОН	2HC1	Yellowish powder MS APCI (m/z): 267 [M+H]+
30	7-13	ис-Д-Йии.	СН₂ОН	Free form	Colorless oil MS APCI (m/z): 247 [M+H]+
	7-14	H ₃ C N N N N N N N N N N N N N N N N N N N	СН₂ОН	2HC1	Pale yellowish solid MS·APCI(m/z): 269[M+H]+
35	7-15	NC-N-N-N-	CH ₂ OH	2HC1	Colorless powder MS·APCI(m/z): 247[M+H]+
40	7-16	∑N N N N	СН₂ОН	2HC1	Colorless solid MS·APCI(m/z): 247[M+H]+
45	7-17	$O_2N- \overbrace{ \begin{array}{c} \\ \\ \end{array}}_N - N$	CH₂OH	2HCl	Yellowish powder M\$ APCI(m/z): 267[M+H]+
50	7-18	NO ₂	CH ₂ OH	2HC1	Pale yellowish solid MS APCI(m/z): 267[M+H]+

Table 5 (Continued)

		,	COMELMACA	-1
Reference Example No.	R2-X-	R1	Salt	Physical properties, etc.
7-19	N= N-1	Me	2HC1	Colorless resin state MS·APCI(m/z): 207 [M+H]+
7-20	O Num	Me	Free form	Powder MS APCI(m/z): 311
7-21	CT _m -	Me		
7-22	H'C. O Bry	Me		
7-23	r O fr	Me		
8-1	N CH3	н	Free form	Colorless resin MS·APCI(m/z): 207 [M+H]+
8-2	Br N CH3	Н	free form	Colorless crystal Melting point: 109-112°C
8-3	N N CH3	Н	Free form	Pale brownish resin MS·APCI(m/z): 207 [M+H]+
8-4	NC NCH3	Н	Free form	Colorless crystal Melting point: 85-87°C

Table 6

	Table 0						
	R ² -X		NH ₂				
Reference Example No.	R2-X-	R ¹	Salt	Physical properties etc.			
9-1	02N-_N-On.	Н	HC1	Colorless crystal Melting point: 271°C			
9-2	NC-{\rightarrow\displaysist}	H	HC1	Colorless crystal Melting point: 289°0			
9-3	$F \xrightarrow{F} $	н	HC1	Colorless crystal Melting point: 253-254°C			
9-4	NO ₂	H	HC1	Pale yellowish crystal Melting point: 230°C			
9-5	CN CN	H	Free form	Colorless crystal Melting point: 70-72°C			
9-6	N- of	H	Free form	Colorless crystal Melting point: 58-59°C			
9-7	Br - NOW	Н	HC1	Colorless crystal Melting point: 284°((decomposed)			
9-8		H	HC1	Colorless crystal Melting point: 279-280°C (decomposed)			
9-9	H ₂ C N	Н	HC1	Colorless crystal Melting point: 275°((decomposed)			
9-10	H ₃ C, O	н	HC1	Colorless crystal Melting point: 275-276°C (decomposed)			
9-11		H	HC1	Colorless crystal Melting point: 194°C			
9-12		H	Free form	Pale yellowish crystal Melting point: 222-223°C			

Table 6 (Continued)

		Tabl	e o	(Continu	ea)
5	Reference Example No.	R2-X-	R1	Salt	Physical properties, etc.
	9-13	CI ZN OW.	Н	Free form	Crystal Melting point: 91-94°C MS APCI(m/z): 229,227
10	9-14	N Com.	Н	Free form	Powder MS·APCI(m/z): 229,227
15	9-15	CH,	H	Free form	Powder MS·APCI(m/z): 223
	9-16	() Om.	Н	free form	Powder MS·APCI(m/z): 193
20	9-17	CI NO.	Н	Free form	Powder MS·APCI(m/z): 229,227
25	9-18	H ₁ C _{-O} , N	Н	-	
	9-19	NOW	Н	Free form	Oil
30	9-20	CI LN LOW.	Н		
35	9-21	(N) CON	н		·
	9-22	H ₂ C-S N N	H	Free form	Colorless powder MS APCI (m/z): 240 (M+H+)+
40	9-23	FXNLow	Н		
45	9-24	H ₂ C N	H	Free form	Powder MS·APCI(m/z): 222
40	9-25	N CN	н	free form	Oil
50	9-26	CI N. N. Om.	Н	Free form	Powder MS-APCI(m/z): 262,260
	9-27	N. N. OHI	Н	Free form	Powder MS·APCI(m/z): 194

Table 6 (Continued)

		143	ore a	(Coner	nueu)
5	Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
10	9-28	H ₂ C N O	н	Free form	Oil MS APCI(m/z): 320
	9-29	Br N Om	Н	Free form	Powder MS ·APCI (m/z): 356,354
15	9-30	N.W. John	H	Free form	Powder MS·APCI(m/z): 270
20	9-31	(Intom.	Н	Free form	Powder MS·APCI(m/z): 243
	9-32	Q's N Som	H	free form	Oil
25	9-33	Om.	Н	form	Powder MS APCI(m/z): 237
30	9-34	Cz Cz	H	HC1	Colorless crystal Melting point: 215-218°C MS APCI(m/2): 217[M+H]
35	9-35	F CN OW	Н	Free form	Yellowish oil
40	9-36	CV F	Н	Free form	Yellowish oil
	9-37	- FOO	н	Free form	Yellowish oil
45	9-38	NC John	н	free form	Colorless oil
50	9-39	F CN	H	Free form	Colorless oil
55	9-40	H ₃ C CN	н	HC1	Colorless crystal Melting point: 253-254°C MS APCI(m/z): 231[M+H]
					MS WLCT (111/5); 521 [MAL)

Table 6 (Continued)

5	Reference Example No.	R²-X-	R ¹	Salt	Physical properties, etc.
	9-41	P CN	H	HC1	Pale green melting point: 270-285°C MS APCI(m/z): 235[M+H]
10	9-42	Br CN	Н	HCl	Colorless crystal melting point: 283-284°C MS APCI(m/z): 297, 295[M+H]
15	9-43	H ₃ C ₁ O CN	Н	HC1	Colorless crystal melting point: 246-247°C MS APCI(m/z): 247[M+H]
20	9-44	CI CN OW.	н .	HC1	Colorless crystal melting point: 285-294°C MS APCI(m/z): 251[M+H]
25	9-45	# 	Н	HC1	Colorless crystal melting point: >300°C MS APCI(m/z): 297, 295[M+H]
	9-46		Н	free form	Pale brownish semi-solid MS APCI (m/z): 194 [M+H] IR(cm-1): 3351
30	9-47	0 ₂ N-________\	Ħ	HC1	Yellow brownish crystal melting point: 238-240°C
35	9-48	NH ₂	Н	HC1	Pale brownish crystal melting point: 180°C (decomposed)
	9-49	HE S	н	Free form	
40	9-50		H	Free form	
45	9-51	HC . H	H	Free form	
50	9-52		Н	Free form	
55	9-53	Hic S	H	Free form	

Table 6 (Continued)

5	Reference Example No.	R²-X-	R1	Salt	Physical properties, etc.
10	9-54	H ₂ C.	Н	Free form	
10	9-55	H _i C _N -CH _i	H	Free form	
15	9-56		н	Free form	
20	9~57	H,C.,CR,	H	Free form	
25	9~58	02N	н	HC1	Pale brownish powder MS APCI(m/z): 238 [M+H]+
	9-59	NCNC-	Н	HC1	Colorless powder MS APCI(m/z): 218 (M+H)+
30	9-60	F N	Н	HC1	Colorless crystal melting point: 234~ 235°C (decomposed)
35	9-61	CN CN	н	HC1	Colorless crystal melting point: 126°C
40	9-62	Br ~ N	н	HC1	Pale yellowish crystal melting point: 206- 207°C (decomposed)
45	9-63	H ₃ C s N	Н	HC1	Pale yellowish crystal melting point: 148- 150°C (decomposed)
	9-64	N	Н	HC1	Colorless crystal melting point: 189- 191°C (decomposed)

Table 6 (Continued)

	Reference			·	
5	Example No.	R2-X-	R ¹	Salt	Physical properties, etc.
10	10-2	NO ₂	Me	Free form	Colorless liquid MS·APCI(m/z): 252[M+H]+
15	10-3	NC-\(\bigs_N^{\displaysis}\)	Me	free form	Colorless crystal Melting point: 73-76°C
	10-4	NO ₂	Me	Free form	Colorless liquid MS·APCI(m/z): 252[M+H]+
20	10-5	NC-_NC	Me	Free form	Colorless crystal Melting point: 88-89°C
25	10-6	O_2N O_2	Me	Free form	Colorless crystal Melting point: 90-94°C
30	10-7	Br—	Me	Free form	Colorless crystal Melting point: 97-100°C
35	10-8		Me	Free form	Colorless crystal Melting point: 150-154°C
		I			

Table 7

	Table 7							
	R ² -X-NH ₂							
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.				
11-1	CH ₃	Н	HC1	Colorless solid Melting point: 150-153°C MS·APCI(m/z): 247 [M+H]+				
11-2		Н	2HC1	Colorless crystal Melting point: 294- 295°C				
11-3	—µ Ju.	н	Free form	Colorless crystal Melting point: 185.5-186°C				
11-4	NH NH	Н	HC1	Colorless solid Melting point: >300°C MS·APCI(m/z): 219 [M+H]+				
11-5		Н	free form	Colorless solid Melting point: 163-166°C				
11-6	CH,	Н	Free form	Colorless liquid MS-APCI(m/z): 239 [M+H]				
11-7	CH ₃	н	Free form	Colorless liquid MS·APCI(m/z): 262 [M+H]				
11-8	N~ CH ₃	н	Free form	Colorless liquid				
11-9	CH ₃	H	Free form	Colorless liquid				
11-10	H ₃ C N	н	Free form	Liquid MS·APCI(m/z): 171 [M+H]				

Table 7 (Continued)

				,	
5	Reference Example No.	R²-X-	R ¹	Salt	Physical properties, etc.
	11-11	H ₃ C N N N N N N N N N N N N N N N N N N N	Н	Free form	Pale yellowish oil MS APCI(m/2): 213
10	11-12	H ₃ C N	Н	Free form	Colorless oil MS APCI(m/z): 241 [M+H]+
15	11-13	H ₃ C N	Н	Free form	Pale yellowish oil MS APCI(m/z): 213
20	11-14	H ₃ C N W	Н	HCl	Colorless liquid MS ·APCI (m/z): 227 [M+H]+
25	11-15	H ₃ C N	н	Free form	Pale yellowish oil MS APCI(m/z): 229
30	11-16	H ¹ C N	H	Free form	Colorless oil MS·APCI(m/z): 253 [M+H]+
35	11-17	H ₂ N	H	HI	Colorless powder MS APCI(m/z): 143[M+H]+
	11-18	H ₃ C — H	Н	Free form	Colorless crystal MS APCI(m/z): 157
10	11-19	H ₃ C N	Н	Free form	Colorless crystal MS·APCI(m/z): 171
is	11-20	H³C N H	Н	free form	Colorless crystal MS·APCI(m/z): 199
	11-21	H ₂ C \ N \ N \ CH ₂ O	Н	Free form	Colorless crystal MS·APCI(m/z): 185
50	11-22	H,C CH, O	Н	Free form	Colorless crystal Melting point: 142°C (Decomposed) MS·APCI(m/z): 199[M+H]+

Table 7 (Continued)

5	Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
	11-23	H ₃ C N	H	Free form	Colorless oil MS APCI(m/z): 185
10	11-24	H ₃ C N	Н	Free form	Colorless oil MS·APCI(m/z): 199
15	11-25	H,C'O N,C	Н	Free form	Colorless resin MS APCI(m/z): 229[M+H]+
	11-26	HIC D HIC	Н	Free form	Colorless resin MS·APCI(m/z): 229[M+H]+
20	11-27	H3C Q H3C	Н	Free form	Colorless resin MS·APCI(m/z): 243[M+H]+
25	11-28	H ₂ C O CH ₂	H	Free form	Colorless cil MS·APCI(m/z): 215
	11-29	HO N N N N N N N N N N N N N N N N N N N	Н	Free form	Colorless oil MS·APCI(m/z): 215
30	11-30	H,C , N , W	Н	Free form	Colorless resin MS·APCI(m/z): 229[M+H]+
35	11-31	HIC HIC	H	Free form	Colorless resin MS·APCI(m/z): 271[M+H]+
	11-32	HSC NAME	Н	Free form	Colorless resin MS·APCI(m/z): 243[M+H]+
40	11-33	N Yuu.	Н	Free form	Colorless resin MS·APCI(m/z): 197[M+H]+
45	11-34	H ₃ C	н	Free form	Pale brownish resin
50	11-35	HJC N N	Н	Free form	Pale brownish resin
	11-36		Н	Free form	Pale brownish resin

Table 7 (Continued)

Reference Example No.	R ² -X-	R1	Salt	Physical properties, etc.
11-37	H ₃ C \	H	Free form	Pale brownish resin
11-38		Н	Free form	Pale brownish resin

Table 8

	Table 8							
	R ² -X-\square MH ₂							
eference Example No.	R2-X-	\mathbb{R}^1	Salt	Physical properties, etc.				
. 12-1	C:v-Jun	H	Free form	Colorless oil MS APCI(m/z): 197 [M+H]+				
12-2	HO N HOW	Н	Free form	Colorless liquid				
12-3	H ₃ C ⁻⁰ N-Jer	Н	Free form	Pale yellowish oil MS·APCI(m/z): 241				
12-4		Н	free form	Colorless oil MS APCI(m/z): 225 [M+H]+				
12-5	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	H	Free form	Colorless oil MS APCI(m/z): 211 [M+H]+				
12-6	H ₃ C N N	Н	Free form	Colorless oil MS·APCI(m/z): 225 [M+H]+				
12-7	H ₃ C N N	н	Free form	Colorless oil MS APCI(m/z): 239 [M+H]+				
12-8	H ₃ C CH ₃	Н	Free form	Colorless liquid MS·APCI(m/z): 267[M+H]+				

Table 8 (Continued)

			- ,	,	
5	Reference Example No.	R²-X-	R1	Salt	Physical properties, etc.
	12-9	H ₃ C N	Н	Free form	Colorless liquid MS-APCI(m/z): 269[M+H]+
10	12-10	H ₂ N N N	Н	Free form	Colorless oil MS·APCI(m/z): 254
15	12-11	H ₂ N N N N	Н	HC1	Colorless oil MS-APCI(m/z): 254 [M+H]+
20	12-12	H³C, N—N—In	Н	2HC1	Colorless powder MS·APCI(m/z): 254[M+H]+
25	12-13	H ² C N N N N N N N N N N N N N N N N N N N	Н	HC1	Colorless resin MS·APCI(m/z): 310 [M+H]+
	12-14	H3C N N N	н	Free form	Colorless solid MS·APCI(m/z): 240
30	12-15	H ₃ C N N N N N N N N N N N N N N N N N N N	H	2HC1	Colorless powder MS·APCI(m/z); 254[M+H]+
35	12-16	H ³ C N N N	н	2HC1	Colorless powder MS·APCI(m/z): 268[M+H]+
40	12-17	HO V N N Jun.	н	2HC1	Colorless powder MS APCI(m/z): 256[M+H]+
	12-18	H ₃ C N N N	н	Free form	Colorless powder MS·APCI(m/z): 254 (M+H)
45	12-19	H³C N N N N N N N N N N N N N N N N N N N	H	Free form	Colorless solid Melting point: 93-96°C
50	12-20	H ₃ C N N N	Н	Free form	Colorless solid Melting point: 242-245°C

Table 8 (Continued)

Table 8 (Continued)						
Reference Example No.	R ^z -X-	R1	Salt	Physical properties, etc.		
12-21	H ₃ C N N N N N N N N N N N N N N N N N N N	Н	Free form	Colorless liquid MS APCI (m/z): 282 [M+H]		
12-22	H ₃ C N N	н	form	Colorless solid Melting point: 173-176°C		
12-23	H ₃ C N N	Н	Free form	Colorless solid Melting point: 135-137°C		
12-24	H,C N-Jun	Н	Free form	Colorless crystal Melting point: 90-92°C		
12-25	H ₃ C S-N N-Jhm.	н	free form	Colorless crystal Melting point: 152-153°C		
12-26	H ₃ C _M ,	н	Free form	Colorless liquid MS·APCI(m/z): 241 [M+H]		
12-27	. ON Jun.	Н	free form	Colorless crystal Melting point: 75-80°C		
12-28	N-Hur.	н	Free form	Colorless crystal Melting point: 170-173°C		
12-29	O ₂ N N N	Н	form	Colorless oil MS APCI(m/z): 290 [M+H]+		
12-30	Qu'yu.	Н	HC1	Pale brownish solid Melting point: 230-233°C		
12-31	N N Jun.	Н	2HC1	Pale yellowish solid MS·APCI(m/z): 246[M+H]+		
12-32	ON This	Н	Free form	Colorless solid Melting point: 150-155°C		

Table 8 (Continued)

	Table 5 (continued)				
5	Reference Example No.	R ² -X-	R1	Salt	Physical properties, etc.
10	12-33	SI NJIII	H	free form	Colorless solid Melting point: 65-69°C
	12-34		H	free form	Colorless solid Melting point: 166-170°C
15	12-35		Н	Free form	Colorless oil MS APCI (m/z): 293 [M+H]+
20	12-36	CH3O	Н	free form	Colorless powder MS·APCI(m/z): 315 [M+H]+
25	12-37		Н	Free form	Colorless solid Melting point: 185-189°C
30	12-38	CH ₃	Н	Free form	Colorless liquid MS·APCI(m/z): 302 [M+H]
	12-39	CI-NN-	Н	Free form	Colorless crystal Melting point: 131-132°C
35	12-40	CH3O-_N_N-_	Н	Free form	Colorless solid Melting point: 81-83°C
40	12-41		н	Free form	Colorless solid Melting point: 185-189°C
45	12-42		Н .	2HC1	Colorless powder MS-APCI(m/z): 290[M+H]+
50	12-43		н	HC1	Colorless solid MS·APCI(m/2): 356(M+H]+

Table 9 (Continued)

	Table 8 (Continued)						
Reference Example No.	R ² -X-	R1	Salt	Physical properties, etc.			
12-44	JOYNON-Aur.	H	free form	Colorless crystal Melting point: 59-60°C			
12-45	O N N Jum	Н	Free form	Colorless liquid MS-APCI(m/z): 302			
12-46	H ₃ C _M ,	Н	Free form	Colorless liquid MS·APCI(m/z): 330 [M+H]			
12-47		Н	Free form	Colorless powder MS-APCI(m/z): 301			
12-48	H ₃ C CH ₃	Н	Free form	Colorless liquid MS·APCI(m/z): 358			
12-49	N O NAME.	Н	Free form	Colorless crystal Melting point: 120-121°C			
12-50	NC NO	Н	Free form	Pale yellowish crystal Melting point: 119-120°C			
12-51	Br-NONN	н	Free form	Colorless crystal Melting point: 144-145°C			
12-52	o'n-	H	Free form	Yellowish crystal Melting point: 140-141°C			
12-53		н	Free form	Colorless crystal Melting point: 110-111°C			
12-54		Н	HC1	Colorless crystal Meltingpoint: 97-°C MS APCI(m/z): 324 [M+H]+			
12-55		Н	Free form	Colorless solid Melting point: 245-248°C			

Table 8 (Continued)						
Reference Example No.	R ² -X-	\mathbb{R}^1	Salt	Physical properties, etc.		
12-56	O I N N Jum	H	Free form	Colorless solid Melting point: 202-205°C		
12-57	O'LOT	Н	Free form	Colorless crystal Melting point: 150-153°C		
12-58	N N N N N N N N N N N N N N N N N N N	Н	Free form	Colorless liquid MS·APCI(m/z): 317 [M+H]		
12-59	S IN NOW	Н	Free form	Colorless crystal Melting point: 158-162°C		
12-60	CH3 N THE	Н	Free form	Colorless liquid MS-APCI(m/z): 319 [M+H]		
12-61		н	HC1	Colorless powder MS·APCI(m/z): 325 [M+H]+		
12-62		H	free form	Colorless crystal Melting point: 148-150°C		
12-63		H	Free form	Colorless powder MS·APCI(m/z): 331 [M+H]+		
12-64		Е	free form	Colorless resin MS-APCI(m/z): 364 [M+H]+		
12-65	CH, NATO	н	Free form	Colorless oil MS-APCI(m/z): 345 [N+H]+		
12-66	CH, CH,	Н	Free form	Colorless oil MS·APCI(m/z): 358 [M+H]+		
12-67	O~i~~	Н	Free form	Colorless crystal Melting point: 70°C		

Table 8 (Continued)

5		R ² -X-	\langle	NH ₂	
10	Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
	12-68		Н	Free form	Colorless crystal Melting point: 188-190°C
15	12-69		Н	2HC1	Colorless crystal Melting point: 180°C (Decomposed) MS·APCI(m/z): 331 [M+H]+
20	12-70	Oh Oh	Н	form	SligHtly brownish crystal Melting point: 214-216°C
25	12-71	\$-0-6	н	Free form	Colorless liquid MS APCI(m/z): 378[M+H]+
30	12-72	s Nam.	н	HCl	Colorless powder MS·APCI(m/z): 229 [M+H]+
	12-73	"°	Н	form	Colorless oil MS APCI(m/z): 241
35	12-74	H³C O N M	Н	Free form	Colorless crystal MS APCI(m/z): 241
40	12-75	HN N Jun.	H	Free form	
45	12-76	H ₂ C-N N	H	Free form	Colorless oil MS·APCI(m/z): 240
••	12-77	٦٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠٠	Н	Free form	Colorless powder MS·APCI(m/2): 284[M+H]+
50	12-78	H ₃ C-N _{CH3}	Н	Free form	Pale yellowish crystal Melting point: 99-104°C MS·APCI(m/z): 283[M+H]+
55	12-79	H'c~}-0\	Н	form	Colorless resin MS·APCI(m/z): 389[M+H]+

Table 8 (Continued)

	Table o (continued)					
Reference Example No.	R2-X-	R1	Salt	Physical properties, etc.		
12-80	H,C-D-Q-J.	Н	Free form	Colorless resin MS APCI (m/z): 317 [M+H]+		
12-81	H _S C-0	Н	Free form	Colorless powder MS APCI(m/z): 275[M+H]+		
12-82	H ₂ N C	Н	Free form	Colorless foam		
12-83	H,C, 17 11	Н	Free form	Pale brownish resin		
12-84	H,C-S TON	Н	Free form	Pale brownish resin		
12-85	но	Н	Free form	Pale brownish resin		
12-86	H ₃ C O O N	Н	Free form	Colorless powder MS APCI(m/z): 275[M+H]+		
12-87	H'C \ COM	Н	Free form	Colorless powder MS APCI(m/z): 289[M+H]+		
12-88	HO	Н	HC1 .	Colorless solid MS APCI(m/z): 261 [M+H]+		
12-89	HIN-STONY	Н	HC1	Colorless solid Melting point: 277-279°C MS·APCI(m/z): 324 [M+H]+		
12-90	H,cc.o	H	HC1	Colorless solid MS·APCI(m/z): 289 [M+H]+		
12-91		н	Free form	Colorless crystal MS-APCI(m/z): 274		
12-92	"L° ((()), L	Н	Free form	Pale brownish resin		
12-93	H,C. J. O. J.	H	Free form	Pale brownish resin		

Table 8 (Continued)

D-f				
Reference Example No.	R²-X-	R ¹	Salt	Physical properties, etc.
12-94	H,C>o^Wy	H	Free form	Pale brownish resin
12-95	" Lange of Don's	Н	Free form	Pale brownish resin
12-96	""CT" (CO-T"	Н	Free form	Pale brownish resin
12-97		Н	Free form	Colorless crystal Melting point: 152-153°C
13-1		Н	free form	Brownish oil MS APCI(m/z): 221 [M+H]+
13-2		Н	free form	Pale yellowish powde MS APCI(m/z): 221 [M+H]+
13-3	H ₃ C N H	Н	Free form	Pale yellowish oil MS APCI(m/z): 237 [M+H]+
13-4	at I	H	Free form	Brownish powder MS·APCI(m/z): 226 [M+H]+
13-5	H,c XX T	Н	Free form	Brownish oil MS·APCI(m/z): 240 [M+H]+
13-6	N T N TW.	Н	free form	Brownish oil MS APCI(m/z): 227 [M+H]+
13-7	но-СУМ	Н	HBr	Fale brownish powder MS·APCI(m/z): 261 [M+H]+
13-8		Н	HI	Yellowish powder MS·APCI(m/z): 204 [M+H]
13-9	NC O	Н	HI	Yellowish powder MS·APCI(m/z): 229 [M+H]
13-10		Н	HI	Yellowish powder MS·APCI(m/z): 238 [M+H]

Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
13-11	CYNO ₂	Н	Free form	Yellowish powder MS APCI(m/z): 249 [M+H]
13-12	H ₃ C CH ₃	н	Free form	Yellowish powder MS-APCI(m/z): 246 [M+H]
13-13	· Q	H	HI	Yellowish powder MS·APCI(m/z): 194 [M+H]
13-14	s Juni	Н	HI	Yellowish powder MS·APCI(m/z): 210 [M+H]
13-15	O'T	Н	HI	Yellowish powder MS·APCI(m/z): 260 [M+H]
13-16		н	2HI	Yellowish powder MS APCI(m/z): 205[M+H]
13-17		Me	HI	Yellowish powder MS APCI(m/z): 227 [M+H]
13-18	H,C, LN N	н	Free form	Colorless semi-solid MS APCI(m/z): 270 [M+H]
13-19	H,c^^ol	н	Free form	Colorless semi-solid MS APCI(m/z): 312 [M+H]
13-20	H'c~y~	Н	Free form	Colorless resin MS ·APCI(m/z): 298 [M+H]
13-21	O-jor	Н	Free form	Colorless oil MS APCI(m/z): 332 [M+H]
13-22	o the contraction of the contrac	н	HC1	Colorless powder Melting point: >300°C MS APCI(m/z): 336 [M+H]
13-23	0 →N Hyc ^N CH ₁	Н	HI	Brownish powder

Table 8 (Continued)

Reference Example No. 13-24	R ² -X-	R ² H	Salt Free	Physical properties etc.
Q	01001r	H	Froe	
			form	Pale brownish resin
13-25 _н		Н	Free form	Pale brownish resin
13-26 N	, i OOy	н	Free form	Pale brownish resin
13-27	~,000-i	н	Free form	Pale brownish resin
13-28	o'cor	Н	Free form	Pale brownish resin
13-29	01001	н	free form	Pale brownish resin
13-30	1400+	H	Free form	Pale brownish resin
13-31	ynoo!	Н	Free form	Colorless powder MS·APCI(m/z): 342 [M+H]+
13-32	, coor	Н	HI	Colorless powder MS APCI(m/z): 315 [M+H]+
13-33 "	100%	H	ні	Colorless powder MS APCI(m/z): 352 [M+H]+
13-34 N	, COLA	H	HI	Pale brownish powder
13-35	H,C LNH	Н	Free form	Brownish oil
13-36	SIP T	Н	Free form	Brownish oil
13-37	1, Or	H	Free form	Brownish oil

Table 8 (Continued)

5	Reference Example No.	R²-X-	R ¹	Salt	Physical properties, etc.
10	13-38	H.C. S-NH	Н	Free form	Brownish oil
10	13-39	H _{SC} & C	Н	Free form	Brownish oil
15	13-40	H ₂ C-N	Н	Free form	Brownish oil
20	13-41	H,c & DN gr	н	Free form	
	13-42	H,C, S-ONF	н	HI	Brownish powder
25	13-43	H,C, J, ON	н	Free form	
30	13-44	"Control of the control of the contr	н	Free form	
	13-45	"-Clor	н	HI	Brownish powder
35	13-46	H _S C N Y	H	Free form	
40	13-47	H,C CONT	н	Free form	Colorless crystal Melting point: 199-202°C MS APCI(m/z): 332 [M+H]+
45	13-48	H ₂ C ₂	Н	Free form	Pale brownish powder MS APCI(m/z): 275 [M+H]+
	13-49	Mc N To Share	Н	Free form	Colorless powder MS·APCI(m/z): 332 [M+H]+
50	13-50	acolo Or	Н	Free form	Colorless powder
55	13-51	H _I C A	Н	Free form	Colorless powder MS·APCI(m/z): 332 [M+H]+

Table 8 (Continued)

	,			
Reference Example No.	R2-X-	R ¹	Salt	Physical properties, etc.
13-52	"°JOY	H	Free form	Colorless powder MS·APCI(m/z): 333 [M+H]+
14-1	HO—N	Н	HC1	Colorless resin MS·APCI(m/z): 227 [M+H]+
14-2		Н	HC1	Colorless powder MS:APCI(m/z): 213 [M+H]+
14-3		Н	Free form	Pale reddish crystal Melting point: 144-145°C
14-4	OH OH	Н	Free form	Colorless oil MS APCI(m/z): 289 [M+H]+
14-5	H ₃ C N	н	HC1	Colorless powder MS·APCI(m/z): 199 [M+H]+
14-6	H ₃ C N	Н	Free form	Pale yellowish oil MS·APCI(m/z): 171 [M+H]+
14-7		Н	Free form	Colorless oil MS·APCI(m/z): 289 [M+H]+
14-8		Н	2HC1	Brownish powder MS APCI (m/z): 294 [M+H]+

Table 8 (Continued)

Reference Example No.	R ² -X-	R1	Salt	Physical properties, etc.
14-9	HO	Н	Free form	Colorless powder MS-APCI(m/z): 303 [M+H]+
14-10	CH ₃	Н	Free form	Colorless oil MS·APCI(m/z): 302 [M+H]+
14-11		Н	Free form	Colorless oil MS·APCI(m/z)
14-12	NC COMO NO	H	Free form	Colorless crystal Melting point: 188-193°C
14-13	O.N O.W ONT	н	Free form	Pale yellowish crystal Melting point: 194-196°C
14-14		H	Free form	Slightly yellowish resin MS·APCI(m/z): 356 [M+H]+
14-15	NC THE MASS H	H	Free form	Slightly yellowish resin MS·APCI(m/z): 356 [M+H]+
14-16	N N N	н	Free form	Brownish oil MS APCI(m/z): 316 [M+H]+

Claims

1. An aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I]:

$$R^{2}$$
 NH
 CH_{2}
 CO
 A
 CN

wherein A represents -CH2- or -S-,

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R1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group.

X represents -N(R3)-, -O- or -CO-, where R3 represents hydrogen atom or a lower alkyl group, and R2 represents (1) a cyclic group which may be substituted, where the cyclic group portion is

- (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or
- (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or
- (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, wherein R2 is

(1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A mentioned below, where the cyclic group portion is (1) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

(2) an amino group which may have 1 or 2 substituents which are the same or different and selected from the substituents of Group B mentioned below.

Substituents of Group A:

a halogen atom; cyano group; nitro group; oxo group; hydroxy group; carboxy group; oxidyi group; amino group; carbamoyi group; aminosulfonyi group; a lower alkyi group;

a lower alkoxy group; a lower alkanoyl group; a lower alkoxycarbonyl group; a lower alkoxy-substituted lower alkanoyl group;

a lower alkoxycarbonyl-substituted lower alkoxy group;

a lower alkoxycarbonyl-substituted lower alkoxycarbonyl group;

a lower alkylthlo group;

a lower alkvisulfonvi group:

a dl-lower alkylamino-substituted lower alkoxy group;

a di-lower alkylaminocarboxy group;

a lower alkyl group substituted by a group selected from amino group, carbamoyl group, a halogen atom, hydroxy group, carboxy group, a lower alkoxy group and mono- or di-substituted amino group:

a mono- or di-substituted amino group:

a mono- or di-substituted carbamoyl group;

a substituted or unsubstituted lower cycloalky! group;

a substituted or unsubstituted lower cycloalkyi-CO-;

a substituted or unsubstituted lower cycloalkyl-lower alkyl group;

a substituted or unsubstituted phenyl group;

a substituted or unsubstituted phenyl-O-;

a substituted or unsubstituted phenyl-CO-:

a substituted or unsubstituted phenyl-lower alkyl group;

a substituted or unsubstituted phenyl-O-lower alkyl group:

55 a substituted or unsubstituted phenylsuifonyl group;

a substituted or unsubstituted phenyl-lower alkoxy group:

a substituted or unsubstituted phenyl-lower alkoxycarbonyl group;

a substituted or unsubstituted lower cycloalkenyl group;

- a substituted or unsubstituted bloyclic heterocyclic group; a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group;
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O-;
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-, a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-lower alkyl group; and
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group.

Substituents of Group B:

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- a lower alkyl group; a lower alkoxy-substituted lower alkyl group; a lower alkoxycarbonyl-substituted lower alkyl group; a hydroxy lower alkyl group; a carboxy lower alkyl group;
 - a substituted or unsubstituted lower cycloalkyl group;
 - a substituted or unsubstituted lower cycloalkyl-lower alkyl group;
 - a substituted or unsubstituted phenyl group;
 - a substituted or unsubstituted phenyl-lower alkyl group;,
 - a substituted or unsubstituted bicyclic hydrocarbon group; a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group;
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group; and
 - a substituted or unsubstituted bicyclic heterocyclic group-lower alkyl group.
- 3. The compound according to Claim 2, wherein when the "substituent selected from the substituents of Group A" is a mono- or di-substituted amino lower alkyl group, a mono-or di-substituted amino group or a mono- or di-substituted carbamoyl group, then the substituent has substituent(s) selected from the substituents of Group C mentioned below; when the "substituent selected from the substituents of Group A" is a substituted lower cycloalkyl group, a substituted lower cycloalkyl-CO-, a substituted lower cycloalkyl-lower alkyl group, a substituted phenyl group, a substituted phenyl-O-, a substituted phenyl-CO-, a substituted phenyl-lower alkyl group, a substituted phenyl-Olower alkyl group, a substituted phenylsulfonyl group, a substituted phenyl-lower alkoxy group, a substituted phenyl-lower alkoxycarbonyl group, a substituted lower cycloalkenyl group, a substituted bicyclic heterocyclic group, a substituted monocyclic 5- or 6-membered heterocyclic group, a substituted monocyclic 5- or 6-membered heterocyclic group-O-, a substituted monocyclic 5- or 6-membered heterocyclic group-CO-, a substituted monocyclic 5- or 6-membered heterocyclic group-CO-lower alkyl group or a substituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group, then the substituent has substituent(s) selected from a halogen atom, cyano group, nitro group, exe group and the substituents of Group C mentioned below; and when the "substituent selected from the substituents of Group B" is a substituted lower cycloalkyl group, a substituted lower cycloalkyl-lower alkyl group, a substituted phenyl group, a substituted phenyl-lower alkyl group, a substituted bicyclic hydrocarbon group. a substituted monocyclic 5- or 6-membered heterocyclic group, a substituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group or a substituted bicyclic heterocyclic group-lower alkyl group, then the substituent has substituent(s) selected from the substituents of Group C mentioned below.

Substituents of Group C:

- a lower alkyl group; a hydroxy-lower alkyl group; a lower alkanoyl group; a lower cycloalkylcarbonyl group; a lower alkoxy group; a lower alkoxyparbonyl group; a lower alkylsullonyl group; a di-lower alkyl-substituted carbamoyl group; a di-lower alkylamino-aubstituted lower alkanoyl group;
- a substituted or unsubstituted phenyl group;
 - a substituted or unsubstituted phenyl-O-;
 - a substituted or unsubstituted phenyl-CO-;
 - a substituted or unsubstituted phenyl-lower alkanoyl group; a substituted or unsubstituted phenyl-lower alkyl group;
 - a substituted or unsubstituted phenyl-lower alkoxy group;
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group;
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O-; a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-; and
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-substituted amino group:
- 55 (In the substituents of Group C, a substituent in the substituted phenyl group portion or the substituted monocyclic 5- or 8-membered heterocyclic group portion is selected from a ladagen atom, cyang group, nitro group, as group, a lower alkyl group, a lower alklowy group, a lower alklanoyl group and a lower alkoxycarbony group).

- 4. The compound according to any one of Claims 1 to 3, wherein R2 is
 - (1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from the following (i) to (iv)
 - (i) a monocyclic hydrocarbon group having 3 to 7 carbon atoms,
 - (ii) a bicyclic hydrocarbon group having 9 to 11 carbon atoms.
 - (iii) a monocyclic heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and
 - (v) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused; or
 - (2) a substituted amino group.

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15 5. The compound according to Claim 4, wherein R2 is

(1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from pheny group, cyclohexty group, cyclohexty group, cyclohexty group, cyclohexty group, cyclohexty group, an indexing group, an indexident group, a thiolary group, a pyracilidinyl group, a middazolidinyl group, a thiolaryl group, a pyracilidinyl group, a thiolaryl group, a group, an indexident group, a thiolaryl group, an indexident group, a thiolaryl group, an indexident group, and indexident group, an indexident group, and indexident group, an indexident group, an indexident group, and indexident group, and indexident group, an indexident group, an indexident group, and indexident group, an indexident group, and indexident group, and indexident group, an indexident group, and indexident group, an indexident group, and indexident

(2) a substituted amino group.

- 6. The compound according to Claim 5, wherein R2 is
 - (1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from the group consisting of phenty group, cyclohexyl group, a pyrriddinyl group, a tetrazolyl group, a trible group, a thiexpoly group, a thiexpoly group, a thiexpoly group, a pyriddinyl group, a morpholinyl group, a pyriddinyl group, a chlydropyrrolopyldyl group, a quinobyl group, a qui
 - (2) a substituted amino group.
- 45 7. The compound according to Claim 6, wherein R² is
 - (1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from the group consisting of
 - a pyrrolidinyl group, a ploafdyl group, a piparazinyl group, a morpholinyl group, a thlomorpholinyl group, a pyrridyl group, a pyrimidinyl group, an indolinyl group, an isoindolinyl group, a pyrrolopyridyl group, a dihydropyrrolopyridyl group and partially or completely saturated cyclic groups thereof, or
 - (2) a substituted amino group.
 - 8. The compound according to any one of Claims 1 to 3, wherein R2 is
 - a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A' mentioned below, where the cyclic group portion is selected from the group consisting of

a pyrrolidinyi group, a phendyl group, a pherazinyi group, a morpholinyi group, a thiomorpholinyi group, a pyridyi group, a pyrimidinyi group, an indollnyi group, an isiondolinyi group, a pyrrolopyridyi group, a dihydropyrrolopyridyi group and partially or completely saturated cyclic groups thereof, or

(2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from the substituents of Group B' mentioned below.

Substituents of Group A'-

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a halogen atom, cyano group, nitro group, oxo group, carbamolyl group, a lower alklyl group, a lower alkoxy group, a lower alkanoyl group, a lower alkoxyearbonyl group, a lower alkoxyeubalituted lower alkyl group, a mono- or di-subalituted emino group, a mono- or di-subalituted carbamoyl group,

a lower cycloalkyl-CO-,

- a substituted or unsubstituted phenyl group,
- a substituted or unsubstituted phenyl-lower alkyl group,
 - a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group.
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O-, and
- a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-,

Substituents of Group B':

- a lower alkyl group, a lower cycloalkyl group, a lower alkoxy-substituted lower alkyl group, a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group.
- The compound according to any one of Claims 1 to 8, wherein X is -N(R3)- or -O-, and R2 is a cyclic group which
 may be substituted.
 - 10. The compound according to any one of Claims 1 to 8, wherein X is -CO-, and R² is (1) a monocyclic, bicyclic or tricyclic nitrogen-containing hotorocyclic group which may be substituted or (2) an amino group which may be substituted, and represented by the formula:

()n-

- 11. The compound according to any one of Claims 1 to 8, wherein X is -CO- or -O-, and A is -CH-
- 12. The compound according to any one of Claims 1 to 8, wherein X is -CO- or -O-, A is -CH₂-, and R¹ is hydrogen atom.
 - 13. The compound according to any one of Claims 1 to 8, wherein X is -CO-, A is -CH₂-, and R¹ is hydrogen atom.
 - 14. The compound according to any one of Claims 1 to 8, wherein X is -CO-, A is -CH₂-, R1 is hydrogen atom, and R2 is a cyclic group which may be substituted.
 - 15. The compound according to any one of Claims 1 to 8, wherein X is -CO-, A is -CH₂-, R¹ is hydrogen atom, and R² is a substituted amino group.
 - 16. The compound according to any one of Claims 1 to 15 which has a partial structure shown below.

17. A compound selected from the group consisting of:

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(S)-2-cyano-1-[trans-4-(δ-nitro-2-pyridylamino)-cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(5-cyano-2-pyridyloxy)cyclohexylamino]acetylpyrrolldine;
(S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(morpholinocarbonyl)cyclohoxylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(5-bromo-2-pyrimidinyloxy)-cyclohexylaminolacetylpyrrolidine:
(S)-2-cyano-1-[trans-4-(5-pyrimidinylaminocarbonyl)-cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(N-ethyl-N-methoxyethylamino-carbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(N-ethyl-N-isopropylamino-carbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(N-methyl-N-butylamino-carbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-[(S)-2-methoxymethylpyrroll-din-1-ylcarbonyl]cyclohexylaminolacetylpyrrollidine:
(S)-2-cyano-1-(trans-4-(3-carbamoy)piperidino-carbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-(3-nitro-2-pyridylamino)-cyclohexylamino]acetylpyrrolidine;
(S)-2-cvano-1-(trans-4-(4-acetylpiperazin-1-vl-carbonyl)cyclohexylaminolacetylpyrrolidine:
(S)-2-cvano-1-ltrans-4-(2-isoIndolinylcarbonyl)-cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-[4-(3-pyrldylcarbonyl)-piperazin-1-ylcarbonyl]cyclohexylaminolacetylpyrrolidine:
(S)-2-cvano-1-(trans-4-[4-(3-thenov])piperazin-1-vl-carbonv[lcvciohexylamino]acetylpyrrolidine:
(S)-2-cyano-1-(trans-4-[4-(4-chlorophenyl)piperazin-1-ylcarbonyl]cyclohexylamino)acetylpyrrolidine;
(S)-2-cyano-1-[traps-4-(cis-2,6-dimethylmorpholino-carbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-evano-1-frans-4-(5-nitro-2-isoindolinyl-carbonyl)cyclohexylaminolacetyloyrolidine:
(S)-2-cyano-1-[trans-4-(piperidinocarbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-(trans-4-(4-carbamoylpiperidino-carbonyl)cyclohexylaminolacetylpyrrotidine:
(S)-2-cvano-1-[trans-4-(1-pyrrolidinylcarbonyl)-cyclohexylaminolacetylpyrrolidine:
(S)-2-cyano-1-[trans-4-(4-cyclopropylcarbonyl-piperazin-1-ylcarbonyl)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-ftrans-4-(4-propionylpiperazin-1-vi-carbonyl)cyclohexylaminolacetylpyrrolldine:
(S)-2-cvano-1-(trans-4-(1-indoliny/carbony/icvclo-hexylaminolacety/pyrrolidine:
(S)-2-cyano-1-[trans-4-(2,3-dihydro-1H-pyrrolo[3,4-b]pyridin-2-ylcarbonyf)cyclohexylamino]acetylpyrrolidine;
(S)-2-cyano-1-[trans-4-[4-(2-pyrimidInyloxy)-piperidinocarbony|]cyclohexylaminolacetylpyrrolidina
(S)-2-cyano-1-(trans-4-[4-(5-bromo-2-pyrimidinyloxy)-piperidinocarbonylloyclohexylamino)acetylpyrrolidine:
(S)-2-cyano-1-[trans-4-(cis-3,5-dimethyl-4-benzyl-piperazin-1-ylcarbonyl)cyclohexylamino]acetylpyrrolldine;
(S)-2-cyano-1-(trans-4-(4-cyclohexylcarbonylamino-piperidinocarbonyl)cyclohexylamino]acetylpyrrolldine;
(S)-2-cyano-1-(trans-4-(4-(N-phenylcarbamovi)-piperazin-1-ylcarbonylicyclohexylaminolacetylpyrrolldine:
(S)-2-cvano-1-(trans-4-(4-athoxycarbonylpiperazin-1-ylcarbonyl)cyclohexylaminolacetylpyrrolidine;
(S)-2-cyano-1-(trans-4-[4-(2-thienyl)piperidino-carbonyl]cyclohexylamino] acetylpyrrolidine.
(S)-2-cyano-1-ftrans-4-(1,1-dioxoperhydro-1,4-thlazin-4-ylcarbonyl)cyclohexylaminolacetylpyrrolidine:
(R)-4-cyano-3-[trans-4-(5-nitro-2-pyridylamino)-cyclohexylamino]acetylthiazolidine;
(R)-4-cyano-3-[trans-4-(5-cyano-2-pyridyloxy)cyclohexylamino]acetyithlazolidine:
(R)-4-cvano-3-[trans-4-(dimethylaminocarbonyl)cyclohexylaminolacetylthiazolidine:
(R)-4-cyano-3-[trans-4-(2-isoindolinylcarbonyl)cyclchexylamino]acetylthiazolidine;
(R)-4-cyano-3-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylthiazolidine; and
(R)-4-cyano-3-(trans-4-(pyrrolidiny/carbonyl)cyclohexylamino]acetylthiazolidine; or a pharmaceutically ac-
ceptable salt thereof.
```

18. A method for preparing an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [ii:

$$R^2-X$$
 $NH-CH_2-CO-N$
 CN
 CN

wherein A represents -CHo- or -S-,

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R1 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

X represents -N(R³)-, -O- or -CO-, where R³ represents hydrogen atom or a lower alkyl group, and R² represents (1) a cyclic group which may be substituted, where the cyclic group portion represents

- (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or
- (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or
- (2) an amino group which may be substituted.

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or a pharmaceutically acceptable salt thereof, which comprises reacting a compound represented by the formula fill :

wherein A has the same meaning as defined above and

Z1 represents a reactive residue,

with a compound represented by the formula [III]:

$$R^2-X$$
 NH_2 [III]

wherein R1, X and R2 has the same meaning as defined above, or a salt thereof, and optionally making the product into a pharmaceutically acceptable salt thereof.

19. A method for preparing an aliphatic nitrogen-containing 5-membered ring compound represented by the formula
[i-a]:

$$R^{21}$$
-CO-NH-CH₂-CO-NA [I-a]

wherein A represents -CH2- or -S-,

R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and

R21 represents (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group,

which may be substituted or (2) an amino group which may be substituted, and represented by the formula:

$$\binom{N-}{N}$$

or a pharmaceutically acceptable salt thereof, which comprises reacting a compound represented by the formula [IV]:

wherein A and R¹ have the same meanings as defined above and R² represents a protective group for an amino group, or a salt thereof with the compound represented by the formula (VI):

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wherein R21 has the same meaning as defined above, or a salt thereof to obtain a compound represented by the formula [VII].

$$R^{21}$$
-CO- N - N - CH_2 -CO- N - A [V]]

wherein R¹, R⁴, R²⁴ and A have the same meanings as defined above, or a self thereof, and subsequently removing the protective group for an amino group R⁴, and optionally making the product into a pharmacoutically acceptable self thereof.

- 20. A method for inhibiting dipopticlylpoptidase IV activity by using the compound according to any one of Claims 1 to 17.
- 21. A method for treatment or prophylaxis of a disease, which comprises administering to a patient an effective dose of the compound according to any one of Claims 1 to 17.
- 22. The method for treatment or prophylaxis of a disease according to Claim 21, wherein the disease is expected to be alleviated by inhibiting diperticiple of the disease is expected to
 - 23. The method for treatment or prophylaxis of a disease according to Claim 21, wherein the disease is diabetes.
 - 24. The method for treatment or prophylaxis of a disease according to Claim 21, wherein the disease is type 2 diabetes.
 - 25. Use of the compound according to any one of Claims 1 to 17 as an inhibitor of dipeptidylpeptidase IV.
 - 26. Use of the compound according to any one of Claims 1 to 17 as a pharmaceutically effective ingredient of a medicine.
 - 27. Use of the compound according to any one of Claims 1 to 17 for the preparation of a medicine.
 - 28. The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of a disease that is expected to be improved by inhibiting dipeptidylpeptidase IV activity.
 - 29. The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of diabetes.

- The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of type 2 diabetes.
 A pharmaceutical composition comprising the compound according to any one of Claims 1 to 17 as an effective ingredient.
- The pharmaceutical composition according to Claim 31 wherein the pharmaceutical composition is a dipeptidylpeptidase IV inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.

			PCI/U	501/08803		
Int. 405/ 31/4	A. CLASSPICATION OF SUBJECT MATTER Int. c.1° COTIZOT/16, 401/12, 403/12, 417/12, 409/14, 413/12, 491/048, 405/14, 405/12, 473/04, 495/04, 403/14, 409/12, 417/14, A61K31/4439, 31/506, 31/501, 31/497, 31/5377, 31/428, According to Intraotiental Patent Classification (EVC) According to Intraotiental Patent Classification (EVC) or to both mational classification and EVC					
B. FIELD:	B. FIELDS SEARCHED					
Int. 405/	Minimum documentation recorded (classification system followed by classification synthols) Incl. cl. 2 (07D207/16,401/12, 403/12, 417/12, 417/12, 417/14, 413/12, 491/04e, 405/14, 405/12, 471/04, 495/04, 401/14, 409/12, 417/14, A61K31/4439, 31/506, 31/501, 31/497, 31/3537, 31/498, 31/5377, 31/408, 31/507, 31/407, 31/507, 31/					
Documentat	Documentation searched after than minimum documentation to the extent that such documents are included in the fields searched					
Electronic d CA (S	ata buse consulted during the international search (nar PTN) , REGISTRY (STN) , WPIDS (STN)	ne of data base and, wi	nere practicable, ser	rch terms used)		
c. Docu	MENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where a	propriate, of the relev	ant passages	Relevará to cigim No.		
A	US 6110949 A (Novartis AG), 29 August, 2000 (29.08.00), the whole document (Family:	none)		1-19,27-32		
A	US 6011155 A (Movertis Ad), od January, 2006 (04.01.00), the whole document & US 6124305 A			1-19,27-32		
	documents are listed in the continuation of Box C.	See patent fam				
** decounter dicising the general state of the an which is near consideration to be a princially released. **Exercise decountered the problem of a right with a learn state of the control of the contro			considered novel or cannot be considered to involve an inventive step when the focument is utera later about the step of the document of pasticular relevance; the claimed invention cannot be considered to showle an inventive step when the document is considered to showle an inventive step when the document is combined with one or more other such documents, such			
	ailing address of the ISA/ nose Patent Office	Authorized officer				
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INTERNATIONAL SEARCH REPORT	International application No.
ATTERNATIONAL SEARCH REPORT	PCT/JP01/08803
	101/01/00003
Continuation of A. 31/423, 31/439, 31/401, 21/4709, 31/454, 31/40, 31/519, 31/473, 31/4725, 31/4065, 31/4035, 31/498, 31/41, 277/82, A61P43/00, 3/10,	25,31/427,31/433,31/55, 31/4155,C07K277/06,277/42,
Continuation of B. 31/423, 31/436, 31/	25,31/427,31/433,31/55, 31/4155,C07K277/06,277/42,

Form PCT/ISA/210 (extra sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No. PCT/JP01/08803

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Box I Observations where certain claims were found anscarchable (Continuation	
This international search report has not been established in respect of certain claims und	er Article 17(2)(a) for the following reasons:
1. Claims Nos.: 20-26	
because they relate to subject matter not required to be searched by this Autho	
Claims 20-26 relate to methods for treatment of the	human body by therapy.
2. Claims Nos.:	
because they relate to parts of the international application that do not comply extent that no meaningful international search can be carried out, specifically:	with the prescribed requirements to such an
extent that no meaningful international search can be cattred out, specifically:	
 Claims Nos.: because they are dependent claims and are not drafted in accordance with the s 	second and third contenant of Dule 6 (/a)
Box II Observations where unity of invention is lacking (Continuation of item 2 of This international Searching Authority found multiple inventions in this international ap-	
This insertational Searching Admonty found mutuple investigate in this internations ap	piscation, as ronows:
 As all required additional search fees were timely paid by the applicant, this in claims. 	temational search report covers all searchable
Comma.	
2. As all searchable claims could be searched without effort justifying an addition	al fee, this Authority did not invite payment
of any additional fee.	
3. As only some of the required additional search fees were timely paid by the app	clicant this international search report course
only those claims for which fees were paid, specifically claims Nos.:	and the statement statement report sorters
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 No required additional search fees were timely paid by the applicant. Conseque search report is restricted to the invention first mentioned in the claims; it is on 	utly, this international
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Remark on Protest The additional search fees were accompanied by the appli-	cant's profest.
No protest accompanied the payment of additional search	•
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